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Chapter 3. Health Consequences of Tobacco Use Among Women

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Introduction

This chapter reviews the evidence for a relationship between smoking, as well as exposure to environmental tobacco smoke (ETS), and a wide range of diseases and health-related conditions among women. It begins with a section on the impact of smoking on mortality from all causes combined among women who smoke compared with women who have never smoked. Most of the remainder of the chapter is devoted to the effects of active smoking on specific health outcomes among women, ranging from cancer to bone density. Lung cancer is discussed first because of the strength of its association with smoking and because smoking is responsible for lung cancer becoming the leading cause of cancer death among U.S. women by the late 1980s, a position it continues to hold. Female-specific cancers are discussed next, followed by other cancers. Because coronary heart disease constitutes the major overall cause of death among women and because of the well-established association of smoking with heart disease and stroke, a section devoted to cardiovascular disease appears next. After that, another important cause of smoking-related morbidity and mortality, chronic obstructive pulmonary disease, is discussed. A brief section on sex hormones, thyroid disorders, and diabetes follows. Next reviewed are areas of unique concern among women, namely the effects of smoking on menstrual function and menopause and on reproductive hormones. Other sections review a variety of diseases (e.g., eye disease, gastrointestinal disease) or physiologic effects (e.g., bone density, nicotine addiction) that have been examined in relation to smoking among women. The chapter concludes with sections on the effect of ETS on female lung cancer, heart disease, and reproductive outcomes. Our knowledge base regarding the effects of smoking on women's health has grown enormously since the Surgeon General's first report on women and smoking was published in 1980 (U.S. Department of Health and Human Services [USDHHS] 1980). The physiologic effects of smoking are broad ranging and, in addition to the health risks shared with men who smoke, women smokers experience unique risks such as those related to reproduction and menopause. Since 1980, approximately three million U.S. women have

died prematurely as a result of a smoking-related disease. In 1997 alone, an estimated 165,000 U.S. women died prematurely of a smoking-related disease.

Because numerous experts contributed to this report, with varying preferences for use of terms to report outcome measures and statistical significance, the editors chose certain simplifying conventions in reporting research results. In particular, the term "relative risk" generally was adopted throughout this chapter for ratio measures of association-whether original study results were reported as relative risks, estimated relative risks, odds ratios, rate ratios, risk ratios, or other terms that express risk for one group of individuals (e.g., smokers) as a ratio of another (e.g., nonsmokers). Moreover, relative risks and confidence intervals were generally rounded to one decimal place, except when rounding could change a marginally statistically significant finding to an insignificant finding; thus, only when the original confidence limit was within 0.95 to 0.99 or within 1.01 to 1.04 were two decimal places retained in the reporting of results.

Total Mortality

Women in the United States began regular cigarette smoking in large numbers decades before women in most other countries did; among women born before 1960, adolescent girls took up regular smoking at progressively earlier ages (Burns et al. 1997a) (see Chapter 2). Thus, U.S. women have been at the forefront of an emerging worldwide epidemic of deaths from smoking, and their experience underscores the need to curtail tobacco marketing world-wide. Women in the United States make up approximately 20 percent of women in the developed world. In 1990, they accounted for more than 40 percent of all deaths attributable to smoking among women in developed countries (Peto et al. 1994).

In this section of Chapter 3, the death rate from all causes combined among women who continue to smoke (current smokers) is compared with the rate in those who have never smoked regularly. The risk from smoking depends on the duration of smoking, the number of cigarettes smoked per day, the age of the smoker, and the epidemiologic measure used to assess risk. By all measures, however, risk increased dramatically among U.S. women from the 1950s through the late 1980s. This finding is clearly demonstrated by the results of at least eight large prospective studies from North America.

Age-Specific and Smoking-Specific Death Rates

The largest contemporary study of smoking and mortality in the United States is the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II)-a prospective, epidemiologic study of more than one million adults that was begun by ACS in 1982 (Garfinkel 1985; Stellman and Garfinkel 1986; Garfinkel and Stellman 1988; Thun et al. 1995, 1997a). Descriptions of CPS-II and of other epidemiologic studies discussed in this section are provided in the Appendix to this chapter.

As illustrated in figure 3.1 and Table 3.1, overall death rates in CPS-II were substantially higher among women who currently smoked cigarettes when enrolled than among those who had never smoked regularly (lifelong nonsmokers). The death rate (per 100,000 person-years at risk) among women who smoked was approximately twice that among women who had never smoked in every age group from 45 through 74 years (Table 3.1). Although death rates were lower among women than among men (Figure 3.1), the relationship of smoking to all-cause death rates was similar among women and men. The large size of CPS-II allows death rates to be estimated fairly precisely by gender and smoking status and within five-year intervals of age at the time of follow-up.

CPS-II data on the relationship of smoking and the risk for death from all causes combined are shown in Table 3.1. This relationship was measured in three ways. (1) The death rate, defined as deaths per 100,000 person-years at risk, reflects the absolute probability (risk) of death per year (also see Figure 3.1). (2) Relative risk (RR), defined as the death rate among smokers divided by the rate among those who had never smoked, expresses the risk among smokers as a multiple of the annual risk among those who had never smoked. (3) Rate difference, defined as the death rate

among smokers minus the rate among those who had never smoked, reflects the absolute excess risk for death per year among smokers compared with those who had never smoked. The CPS-II results illustrate that the impact of smoking on deaths from all causes varies at different ages for each of the three measures of risk (Thun et al. 1997c). Beginning at approximately age 45 years, the death rate from all causes was progressively higher among women who smoked than among those who had never smoked (Figure 3.1). The absolute increase in risk associated with smoking became greater with age, as measured by the increase in the rate difference from ages 45 through 84 years (Table 3.1). In contrast, the value for RR associated with any current smoking increased from approximately 1.0 among women younger than 45 years to a maximum of 2.3 at ages 60 through 69 years, then decreased to 1.6 at ages 80 through 84 years (Table 3.1).

Measured in absolute terms, smoking becomes more, rather than less, hazardous with increasing age. Older smokers incur a larger individual risk for dying prematurely from their smoking than do younger smokers, and the total number of smoking attributable deaths is greater among older smokers than among younger smokers. On the other hand, trends in RR reflect first the increase and later the decrease, with age, of the proportionate contribution of smoking to deaths among smokers. In the CPS-II data, the RR associated with smoking among women peaked at 2.3 at ages 60 through 69 years (Table 3.1). The corresponding RR among British male physicians and men in CPS-II who continued to smoke cigarettes was approximately 3.0 at approximately 40 through 60 years of age (Doll et al. 1994; Thun et al. 1997c). The proportionately smaller contribution of smoking to death among older smokers indicated that death rates from factors unrelated to smoking increase even faster at older ages than do the increasing hazards from smoking.

Changes over Time in the Association Between Smoking and All-Cause Death Rates

Changes in women's smoking behavior, particularly the trend up to 1960 among adolescent girls to start smoking at progressively earlier ages, underlie the gradual increase in smoking-associated RR for death among women smokers in the last half-century. A unique longitudinal perspective on how smoking behavior and smoking-specific death rates changed among U.S. women from the late 1950s through the 1980s may be seen by comparing the results of CPS-II with its predecessor, the Cancer Prevention Study I (CPS-I), which was conducted by ACS in 1959-1965 (USDHHS 1989b; Thun et al. 1995, 1997a). In CPS-I, methods of recruitment and follow-up were similar to those in CPS-II (see Appendix to this chapter). In general, women in CPS-I who smoked began to smoke regularly just before, during, or after World War II, and relatively few had smoked for more than 20 years. In contrast, many women enrolled in CPS-II had smoked regularly for 30 to 40 years. Women in CPS-II started smoking in larger numbers at younger ages and, in every age group, the mean number of cigarettes smoked daily at baseline was greater (Thun et al. 1997a,c).

Two major temporal trends are evident in the comparison of age-specific and smoking-specific all-cause death rates in CPS-I and CPS-II. The first trend (Figure 3.2) is that the difference in female age-specific, all-cause death rates (rate difference) between current smokers and women who had never smoked (as reported at enrollment) was much greater in CPS-II than in CPS-I at age 45 years and older. Tables 3.1 (CPS-II) and 3.2 (CPS-I) present age-specific, all-cause death rates among women for the two studies directly standardized to the age distribution of the U.S. population in 1980. The rate difference between women who were current smokers and those who had never smoked almost doubled, from 238.4 in CPS-I (Table 3.2) to 438.5 in CPS-II (Table 3.1). Similarly, the RR associated with current smoking increased from 1.3 (Table 3.2) to 1.9 (Table 3.1). These large increases during the two decades between the two ACS studies in both the rate difference and the RR for U.S. women who smoked reflect the emergence of the full effect of smoking-related deaths among women who were long-term smokers.

The second important difference between CPS-I and CPS-II is the decline in background rates of allcause mortality in the time period between the two studies. This mortality rate difference was largely due to the decline over the past several decades in death rates for cardiovascular diseases-the leading cause of death in the United States among women and men. Table 3.2 (CPS-I) and Table 3.1 (CPS-II) show the age-adjusted, all-cause death rates among smokers and among persons who had never smoked. The all-cause death rate among women who had never smoked

was approximately 50 percent lower for those in CPS-II than for those in CPS-I, but only 22 percent lower among current smokers in CPS-II than among current smokers in CPS-I. This difference largely reflects the decline in death rates for cardiovascular disease over these two decades, and the decline in cardiovascular disease death rates between the two studies was smaller among women who smoked than among women who had never smoked.

Consistency of Temporal Trends Across Studies

Beside the results of CPS-I and CPS-II, other prospective studies since the late 1940s suggested a temporal trend of increasing RR for death from all causes among female smokers and an increasing proportion of deaths attributable to smoking (Figure 3.3). None of these cohort studies (see Appendix to this chapter) was designed specifically to assess a temporal trend in risk. Collectively, however, their results suggested that the all-cause RR associated with current smoking for women was similar across studies and that the RR increased from approximately 1.2 in the 1950s and early 1960s to a range of 1.8 to 1.9 by the 1980s. In the earlier studies, including the British doctors' study (Doll et al. 1980), a large census-based study in Japan (Hirayama 1990), and CPS-I (Thun et al. 1997a), women who smoked had usually begun to smoke regularly less than 20 years before the start of the study. In the more recent studies, including the U.S. Nurses' Health Study (Kawachi et al. 1993a), the Kaiser Permanente Medical Care Program cohort study (Friedman et al. 1997), a study of three U.S. communities (LaCroix et al. 1991), and CPS-II (Thun et al. 1997a), women who reported current smoking had smoked for longer periods of time than they did in the earlier studies. In a recent cohort study, the estimated RR for death from all causes combined was slightly lower (1.7; 95 percent confidence interval [CI', 1.5 to 1.9) than in the other studies (Paganini-Hill and Hsu 1994). Participants in that study, however, were members of the Leisure World retirement community of southern California and were substantially older at the time of enrollment (median age, 73 years) than were the participants in most of the other studies.

The investigators of four studies (Canadian Department of National Health and Welfare 1966; Shurtleff 1974; Cederlöf et al. 1975; USDHHS 1980) measured the excess risk among smokers by calculating the cumulative probability of death ratio, which was defined as the probability of death among smokers divided by the probability among those who had never smoked, over a specified period (Kleinbaum et al. 1982). In studies with prolonged follow-ups and a common end point, the use of this ratio results in a slight underestimation of the RR (Rothman 1986). Thus, these studies are presented separately from the eight studies, including CPS-I and CPS-II, that reported annual death rate ratios (Figure 3.3 and Appendix to this chapter).

The findings in CPS-I, CPS-II, and the other studies generally support the observation that the risk for death from smoking among U.S. women has increased over time. Total mortality by amount smoked also has been reported based on pooled data from three prospective studies conducted in Copenhagen, with initial exams between 1964 and 1992 and follow-up until 1994 (Prescott et al. 1998a). RRs for all-cause mortality increased with amount smoked: compared with persons who had never smoked, the RR was 2.2 (95 percent CI, 2.0 to 2.5) among women who smoked less than 15 g of tobacco per day, 2.7 (95 percent CI, 2.4 to 3.1) among women who smoked 15 to 24 g per day, and 3.6 (95 percent CI, 2.9 to 4.5) among those who smoked 25 g or more per day.

Adjustment for Risk Factors Other than Smoking

Although factors such as the duration of smoking, the number of cigarettes smoked per day, and the age of the smoker strongly influence the association between smoking and all-cause mortality, other demographic and behavioral factors associated with smoking also appear to affect the risks associated with smoking.

In most studies, risk estimates were not adjusted for potential confounders other than age. However, studies in which adjustment was made for other factors found little evidence that the estimates of risk associated with smoking were substantially different after adjustment. Data from the 12-year follow-up of the U.S. Nurses' Health Study showed no real difference between the estimates of RR for death from all causes combined that were adjusted for age alone and

the estimates that were adjusted for age, hypertension, cholesterol, menopausal status, postmenopausal estrogen therapy, and other factors (Kawachi et al. 1993a, 1997b) (Table 3.3).

Among women in CPS-II, values for the RR for death from all causes combined were negligibly different among current smokers aged 30 years or older after adjustment for age, dietary fat and vegetable consumption, physical activity, and aspirin use (ACS, unpublished data) (Table 3.4). Small changes in the RR after multivariate adjustment (Table 3.4) would result in even smaller change in the attributable fraction among persons exposed, assuming that the estimates of RR accurately reflect a causal relationship with smoking. Adjustment for covariates decreased the attributable fraction from 50 to 47 percent of all deaths among current smokers and increased it from 23 to 29 percent among former smokers (Table 3.4). Thus, when adjusted only for age, nearly one-half of all deaths among women who currently smoked and about one-fourth of deaths in former smokers were attributable to smoking. In comparison, the percentage of deaths that would be attributable to smoking among women current smokers in the earlier period of CPS-I was only 21 percent (Table 3.2 and Figure 3.3).

Smoking Attributable Deaths Among U.S. Women

Two approaches have been used to estimate the number of deaths attributable to smoking among U.S. women and to assess how this burden has changed over time. Estimates for the U.S. Public Health Service are produced by the Centers for Disease Control and Prevention (CDC), Office on Smoking and Health, using a computer program-Smoking Attributable Mortality, Morbidity, and Economic Costs (SAMMEC 3.0), which incorporates an epidemiologic measure of risk known as the population attributable risk (USDHHS 1997). These estimates for women take three factors into account: (1) the prevalence of current and former smoking among U.S. women in a particular year, (2) the RR estimates among women in CPS-II during the initial four years of follow-up for selected conditions having a firmly established relationship to smoking, and (3) the total number of deaths coded to these conditions among U.S. women. The SAMMEC estimate has increased from 30,000 in 1965 to 106,000 in 1985 (USDHHS 1989b) and to 152,000 annually during 1990-1994 (CDC 1997). For 1995-1997, the annual SAMMEC estimates for U.S. women averaged 163,000 (CDC, unpublished data). On the basis of recent trends in these estimates, it can be projected that SAMMEC estimates among U.S. women during the years 1998-2000 will average about 170,000 (CDC, unpublished data). Thus, since the last report on the health consequences of smoking among women in 1980, it can be estimated that approximately 3 million deaths among U.S. women have been attributable to smoking (CDC, unpublished data).

An alternate technique was developed by Peto and associates (1994) to provide estimates of deaths from smoking in developed countries, even where reliable data on smoking prevalence are not available. By using the national death rate for lung cancer to index past smoking habits, Peto and associates estimated that smoking caused approximately 14,100 deaths among U.S. women in 1965 and 131,000 in 1985. Although not expected to be exact, the estimates of smoking attributable mortality generated for different countries by use of this method showed that women in the United States and the United Kingdom who have smoked longer than women in other countries are at the forefront of the emerging global epidemic of deaths from tobacco smoking (Peto et al. 1994).

Years of Potential Life Lost

Another measure of the impact of smoking on survival is years of potential life lost (YPLL). Although less commonly used, YPLL takes into account the age at which people die, as well as the total number of deaths. Using the SAMMEC software program (USDHHS 1997), CDC's Office on Smoking and Health estimated YPLL from smoking among U.S. women each year during 1990-1994 on the basis of diseasespecific RRs among women smokers from CPS-II for 1982-1986, mortality data among U.S. women for 1990, and prevalence of current and former women smokers in the United States in 1990-1994 (CDC 1997). Based on survival to life expectancy, the average annual YPLL due to smoking-related deaths from neoplastic, cardiovascular, respiratory, and pediatric diseases was 2,148,000, or about 14 years for each smoking attributable death (CDC, unpublished data). This estimate did not include YPLL due to

exposure to ETS. Other investigators estimated that U.S. white women who were current smokers had a life expectancy in 1986 that was three to seven years less than that of women the same age who had never smoked (Rogers and Powell-Griner 1991). Amultisite, population-based, prospective study of persons aged 65 years or older found that even when level of physical activity was controlled for, women who had ever smoked lived an average of four to five years less than women who had never smoked (Ferrucci et al. 1999). On the basis of these YPLL estimates and the estimated number of deaths among U.S. women attributable to smoking, it can be estimated that since the last report on the health consequences of smoking among women in 1980, from 9 to 41 million years of potential life have been lost by U.S. women because of smoking (CDC, unpublished data).

Effects of Smoking Cessation

Several studies examined the reduction in allcause death rates among women that is related to smoking cessation (USDHHS 1990). In the U.S. Nurses' Health Study, to better estimate the effect of cessation, women with nonfatal coronary heart disease, stroke, or cancer (except nonmelanoma skin cancer) were excluded at baseline and at the beginning of each 2-year follow-up period. The RR for death from all causes combined during the 12-year follow-up was 1.15 (95 percent CI, 1.01 to 1.29) among women who had stopped smoking (Kawachi et al. 1993a, 1997b). This RR was substantially lower than that of 2.04 (95 percent CI, 1.85 to 2.27) among women who continued to smoke (Kawachi et al. 1993a, 1997b). The RR among former smokers decreased progressively with time since smoking cessation; 10 through 14 years after smoking cessation, the RR approached the risk among those who had never smoked (Figure 3.4).

An alternate method of expressing the benefits of smoking cessation is to present the absolute risk for death at various ages during follow-up by grouping women according to age at cessation of smoking. Figure 3.5 shows the cumulative probability that a woman in CPS-II would die during follow-up in 1984-1991 according to smoking status at study entry and, for former smokers, according to age at the time of smoking cessation (ACS, unpublished data). To minimize bias from smoking cessation due to illness, this analysis excluded data from the first two years of follow-up; persons with a history of cancer, heart disease, or stroke at study entry; and persons who had stopped smoking less than two years before enrollment. During the seven-year period, women who were current smokers at baseline had the highest cumulative probability of death during follow-up; those who had stopped smoking, particularly at younger ages, had intermediate risk; and those who had never smoked had the lowest risk. The risk among women who had stopped smoking before age 50 years was only slightly higher than that among women who had never smoked and, over time, the risk became indistinguishable from that among those who had never smoked. However, it should be stressed that the probabilities shown in Figure 3.5 are underestimates of the true cumulative risk for death at any age in the general population because the calculations are based on data from a cohort that included only women who survived and could therefore enter the study and excluded women with cancer, heart disease, or stroke at the time of enrollment, thereby making the study population healthier than the general U.S. population. Nevertheless, Figure 3.5 illustrates the substantial benefits of smoking cessation, the additional benefit for women who stop smoking at a younger age, and the optimal situation of never having started to smoke.

Conclusions

1. Cigarette smoking plays a major role in the mortality of U.S. women.
2. The excess risk for death from all causes among current smokers compared with persons who have never smoked increases with both the number of years of smoking and the number of cigarettes smoked per day.
3. Among women who smoke, the percentage of deaths attributable to smoking has increased over the past several decades, largely because of increases in the quantity of cigarettes smoked and the duration of smoking.
4. Cohort studies with follow-up data analyzed in the 1980s show that the annual risk for death from all causes is 80 to 90 percent greater among women who smoke cigarettes than among women who have never smoked. A

woman's annual risk for death more than doubles among continuing smokers compared with persons who have never smoked in every age group from 45 through 74 years.

5. In 1997, approximately 165,000 U.S. women died prematurely from a smoking-related disease. Since 1980, approximately three million U.S. women have died prematurely from a smoking-related disease.
6. U.S. females lost an estimated 2.1 million years of life each year during the 1990s as a result of smoking-related deaths due to neoplastic, cardiovascular, respiratory, and pediatric diseases as well as from burns caused by cigarettes. For every smoking attributable death, an average of 14 years of life was lost.
7. Women who stop smoking greatly reduce their risk for dying prematurely. The relative benefits of smoking cessation are greater when women stop smoking at younger ages, but smoking cessation is beneficial at all ages.

Cancer

Lung Cancer

When the report to the Surgeon General on smoking and health was published in 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), lung cancer mortality among women was low (approximately 7 deaths per 100,000 women). The 1964 report concluded that evidence suggested a causal association between smoking and lung cancer among women but did not conclude that smoking was a cause of lung cancer among women. Subsequent reports of the Surgeon General reviewed data published after 1964, including both cohort and case-control studies of lung cancer among women, and strongly affirmed a causal relationship (USDHHS 1980, 1982, 1989b, 1990) between smoking and lung cancer among women.

Women started smoking in the 1930s and 1940s, about 20 to 30 years later than men. Thus, the sharp rise in lung cancer mortality that was so apparent among men before 1964 (from 5 deaths per 100,000 in 1930 to 45 deaths per 100,000 in 1964) did not occur until the 1970s among women (USDHHS 1989b). By 1980, when the first Surgeon General's report on women and smoking was released, lung cancer had become the second-leading cause of cancer deaths among women (USDHHS 1980). The lung cancer death rate among white women rose by over 600 percent from 1950 through 1997. This rise was equivalent to an average annual increase of 5.3 percent (Ries et al. 2000). During the 1973-1997 period, the lung cancer death rate among women increased 149 percent, but only 6.5 percent among men (Ries et al. 2000). In 1987, lung cancer surpassed breast cancer as the leading cause of cancer death among women (Figure 3.6), and in 2000, lung cancer accounted for an estimated 1 of every 4 cancer deaths and nearly 1 of every 8 newly diagnosed cancers among women (Greenlee et al. 2000). The estimates for 2000 also indicated that about 74,600 new cases of lung cancer would be diagnosed and that 67,600 deaths from the disease would occur among women (Greenlee et al. 2000).

Lung cancer incidence among women increased by 127 percent from 1973, when ongoing collection of population-based cancer incidence data by the National Cancer Institute (NCI) began, through 1997, when the annual age-adjusted incidence was 43.1 cases per 100,000 women (Ries et al. 2000). In recent years, the rate of increase has slowed-from 9.1 percent per year for 1973-1976 to 0.0 percent per year for 1991-1997. Incidence rates among women may have peaked in the 1990s (Wingo et al. 1999; Ries et al. 2000). Rates among women aged 40 through 49 years and among women aged 50 through 59 years reached a peak in the mid-1970s and late 1980s, respectively, whereas rates remained stable among women aged 60 through 69 years (Wingo et al. 1999). The overall age-adjusted incidence among men has declined steadily since 1987 (Ries et al. 2000). By 1997, the male-to-female ratio for incidence of lung cancer was 1.6:1, a change from 3:1 in 1980. In 1995-1997, the lifetime risk for developing lung cancer was 1 in 17.3 among women.

The overall incidence of lung cancer among black women resembles that among white women. In 1997, the age-adjusted incidence per 100,000 women was 42.6 among blacks and 45.0 among whites (Ries et al. 2000). In contrast,

the incidence among black men was more than 50 percent higher than that among white men. In 1996-1997, lung cancer incidence rates among women younger than age 65 years were higher among blacks than among whites (Figure 3.7). This finding suggested that differences between incidence among black women and white women may increase in the future.

In the United States, the incidence rate for 1990-1997 among Hispanic white women (20.3 per 100,000 women) was one-half that among non-Hispanic white women (45.9) (Ries et al. 2000). The rate among Asian or Pacific Islander women (22.5 per 100,000 women) was also lower than that among white women. Variation exists among subgroups of Asian women. Based on data for 1988-1992, rates were lowest among Japanese women and highest among Vietnamese women: 15.2 per 100,000 among Japanese, 16.0 among Korean, 17.5 among Filipino, 25.3 among Chinese, and 31.2 among Vietnamese women (NCI 1996b). Hawaiian women, however, developed lung cancer at approximately the same rate as did white women (43.1) (NCI 1996b). Incidence rates from California for 1991-1995 were comparable among non-Hispanic black women (48.2) and non-Hispanic white women (50.4), whereas rates among Hispanic women (19.7) and Asian women (21.7) were about 50 percent lower (Perkins et al. 1998). These differences in the incidence rate of lung cancer are likely the result of lower rates of cigarette smoking among Hispanic women and Asian women.

Because of the poor survival associated with lung cancer, mortality parallels incidence for all age and ethnic groups. The 5-year relative survival rates among black women and white women diagnosed with lung cancer in 1989-1996 were 13.5 and 16.6 percent, respectively (Ries et al. 2000). Survival was higher among women with localized disease (52.5 percent), but only 16 percent of cases among women were diagnosed at this early stage. Survival rates declined with age at diagnosis and advanced stage of disease but were higher among women than among men at all ages and stages and for all cell types. Survival rates have changed little in the past 20 years (Ries et al. 2000).

Smoking-Associated Risks

Evidence from Cohort Studies

Six prospective studies, which included more than one million women from four countries, provided data on smoking and risk for lung cancer among women. Many of the results from these studies were described previously (USDHHS 1982, 1989b). All showed significantly higher lung cancer mortality among smokers than among nonsmokers (Table 3.5). Together with case-control studies, these studies demonstrated that lung cancer mortality among women increases with increasing exposure to cigarette smoking, as measured by the number of cigarettes smoked daily, duration of smoking, depth of inhalation, age at smoking initiation, and tar content of the cigarettes smoked (USDHHS 1980, 1982, 1989b). The lower RRs observed among women than among men reflect differences in smoking habits across birth cohorts. Historically, women adopted the smoking habit at a later age than did men, smoked fewer cigarettes per day for fewer years, were less likely to inhale deeply, and were more likely to smoke filter-tipped or low-tar cigarettes (USDHHS 1980).

CPS-I, which was begun in 1959, and CPS-II, which was begun in 1982, enabled examination of changes over time in smoking-associated risk for death from lung cancer. Data from CPS-I and CPS-II confirmed that the epidemic of lung cancer among women was confined largely to smokers. The age-adjusted lung cancer death rate among women who had never smoked was about the same during the two study periods, but among current smokers, it increased nearly sixfold (Table 3.6). In CPS-I, lung cancer mortality was 2 to 3 times higher among women smokers than among women who had never smoked; 20 years later, in CPS-II, mortality was more than 12 times higher. (During this same period, the rate among men increased by a factor of 2.) Women in CPS-II began smoking earlier in life, smoked for more years, and reported inhaling moderately or deeply more often than did women in CPS-I. These findings probably largely explain the higher RR among smokers in CPS-II than in CPS-I, the corresponding greater differences in absolute risk among women smokers and nonsmokers, and the narrowing of the gender gap for these measures over time (Thun et al. 1997a) (Table 3.6).

The risk for lung cancer mortality increases with the number of cigarettes smoked (USDHHS 1989b) (Table 3.5). In CPS-II, the RR for lung cancer death increased from 3.9 among women who smoked 1 to 9 cigarettes per day to 21.4 among women who smoked one to two packs of cigarettes (21 to 39 cigarettes) per day (Thun et al. 1997a). Analyses from a cohort study of subscribers of a large health maintenance organization (HMO) (Kaiser Permanente Medical Health Care Program Study) also showed a RR of 21.7 among women who smoked 20 or more cigarettes per day (Table 3.5). The risk increased 12.0 times among women who smoked for 20 to 39 years and 27.5 times for women who smoked 40 or more years (data not shown) (Friedman et al. 1997).

The age-adjusted RR among current smokers and among persons who had never smoked varies with race and ethnicity. The RR was lower among Asian women (3.2) than among black women (23.5) or white women (18.6) in an HMO cohort study (Friedman et al. 1997). These differences may reflect racial or ethnic differences in dose, duration, and intensity of smoking (Shopland 1995). Cohort studies have not included enough minority women to allow comparison of the dose-response effect of smoking and lung cancer among racial and ethnic groups.

In CPS-II, RRs decreased after cessation of cigarette smoking. The RR for death from lung cancer among women former smokers was about 50 percent lower than that among women current smokers, but it was still higher than that among women who had never smoked (Table 3.5). The RR for lung cancer in both the HMO study and CPS-II decreased with increased duration of smoking cessation (Table 3.7). CPS-II data showed marked reductions in RR within 3 to 5 years after smoking cessation, especially among lighter smokers. However, lung cancer mortality remained higher among women former smokers than among those who had never smoked, even after more than 15 years of smoking cessation (USDHHS 1990).

Evidence from Case-Control Studies

More than 20 case-control studies of smoking and lung cancer that included women have been reviewed (USDHEW 1971, 1979; USDHHS 1982). Table 3.8 presents estimated RRs from 11 studies reported during 1985-1993 from the United States, Canada, and northern Europe. Each of these studies included approximately 100 or more cases of lung cancer among women. Consistent with findings in cohort studies and temporal trends in women's smoking, results of case-control investigations showed an increase in smoking-associated risk for lung cancer during the 1950s through 1970s (USDHHS 1982). A steep upward gradient in risk with the number of cigarettes smoked per day was reported from almost all case-control studies of smoking and lung cancer among women conducted during the 1980s (USDHHS 1989b). The estimated risk for lung cancer among women who smoked 20 or more cigarettes per day relative to nonsmokers (10- to 20-fold excess risk) was remarkably consistent in both hospital- and population-based studies in Europe and North America.

Lung cancer risk increased with the number of years of smoking, and this increase was independent of the number of cigarettes smoked per day (Schoenberg et al. 1989; Osann 1991). The RRs were 2 to 3 among women who smoked for shorter durations (<20 years [Osann 1991], <20 pack-years [pack-years is the number of packs of cigarettes smoked per day multiplied by the number of years of cigarette smoking] [Sellers et al. 1991], or <35 years and <20 cigarettes per day [Schoenberg et al. 1989]) and 8 to 24 among those who smoked for longer durations. The risk for lung cancer was two to four times higher among women who inhaled tobacco smoke frequently and deeply than among those who did not inhale (Potter et al. 1985; Osann 1991) (data not shown).

Age at initiation of smoking is closely associated with the number of years of smoking. Because women who smoked for the longest duration usually began to smoke at younger ages, it is difficult to separate the independent effect of each factor related to lung cancer risk (Thun et al. 1997c). Although a significant increase in risk with early age at smoking initiation was noted in one study of women (Hegmann et al. 1993), other studies showed no such increase after adjustment for duration of smoking (Svensson et al. 1989; Benhamou and Benhamou 1994). A differential effect for age at initiation, independent of the quantity of cigarettes smoked and the duration of smoking, would imply that the lung is more susceptible to the carcinogenic effects of cigarette smoke at a younger age.

Data from case-control studies generally support the association between tar level of cigarettes and lung cancer risk observed in some cohort studies (Stellman and Garfinkel 1986; Garfinkel and Stellman 1988; Sidney et al. 1993; Stellman et al. 1997). Women who smoked nonfiltered cigarettes had higher risk than did women who smoked filter-tipped brands (Pathak et al. 1986; Wynder and Kabat 1988; Lubin et al. 1984; Stellman et al. 1997). Several researchers attempted to account for variation in tar yield over time and by brand of cigarettes. Kaufman and colleagues (1989) examined dose-response relationships by using the average tar content of cigarettes smoked over a specified period. Zang and Wynder (1992) constructed an index of cumulative tar exposure. Both methods showed an increase in lung cancer risk among women with increased exposure to tar. Limitations of studies of tar exposure include use of surrogate measures for tar in some studies (e.g., presence or absence of a filter), use of a machine-derived tar yield of specific brands at a certain time or during a short interval, and failure to account for compensatory changes in smoking habits (e.g., increased depth of inhalation or number of puffs). Underestimation of actual exposure to tar levels in human-based or machine-derived results of Federal Trade Commission (FTC) testing methods to date has long been a concern (National Cancer Institute 1996a; Djordjevic et al. 2000).

Few case-control studies reported data on variation in smoking-associated risk by race or ethnicity. In a hospital-based study, the odds for lung cancer were higher among black women than among white women at each level of tar exposure (Harris et al. 1993). Although RRs were generally higher among black women across all histologic types of lung cancer, the differences were greater for the types most strongly associated with smoking. Humble and coworkers (1985) found no significant differences between non-Hispanic white women and Hispanic women in dose-response relationships. A case-control study examined risk for lung cancer by race and ethnicity among women in Hawaii who had ever smoked (Le Marchand et al. 1992). Relative to Japanese women, RRs were higher among Hawaiian (1.7), Caucasian (2.7), and Filipino (3.7) women and lower among Chinese women (0.4), after adjustment for pack-years of smoking and age. However, these results were not statistically significant. Differences across ethnic groups in the reporting of smoking habits or the intensity of smoking may be responsible for some of the observed differences in lung cancer risk.

Case-control studies of lung cancer risk among women former smokers were described previously (USDHHS 1990). Retrospective investigations reported since 1985 all showed lower risk among former smokers than among current smokers (Table 3.8). Risk declined within 5 years of smoking cessation, varied with the level of previous exposure, but remained higher than the risk among those who had never smoked, even after 20 years of abstinence. The rate of decline in risk with years of abstinence is not well characterized because of the small number of former smokers, particularly long-term former smokers, in most case-control studies.

Differences by Gender

Although the RR for death from lung cancer among women current smokers increased over time (Thun et al. 1997a), all but one of the six major cohort studies (Table 3.5) showed lower RRs among women than among men (Kaiser Permanente Medical Care Program Study). The difference is believed to result from the time lag in smoking initiation among women and thus the lower cumulative exposure to smoking among birth cohorts of women (Burns et al. 1997b). In CPS-I, the RRs among women smokers were approximately one-fifth as high as those among men (Thun et al. 1997a). Among women smokers in CPS-II, death rates and RRs were about one-half those among men smokers in CPS-II and were equal to those among men 20 years earlier in CPS-I (Thun et al. 1997a). Differences in RR may be due to differences between women and men in duration and intensity of smoking within each age- and quantity-specific stratum or to residual confounding within these large strata (Thun et al. 1997c). Cohort studies generally have not been large enough to allow comparison of RR for subgroups of women and men of exactly comparable age and smoking exposure. However, within categories defined by age, number of cigarettes smoked, and duration of smoking in years that were examined using CPS-II data, men generally had higher lung cancer death rates than did women (Thun et al. 1997a) and the rate ratios associated with smoking were generally higher among men than among women (Thun et al. 1997b). A pooled analysis of data from three prospective population-based studies conducted in the area

of Copenhagen, Denmark (13,444 women and 17,430 men), examined risk for lung cancer by pack-years of smoking and gender. After adjustment for pack-years of smoking, the ratio of female to male smokers' RRs for developing lung cancer was 0.8 (95 percent CI, 0.3 to 2.1) (Prescott et al. 1998b). On the other hand, results from the HMO study found that risk was higher among female heavy smokers than among male heavy smokers in every age group (Friedman et al. 1997).

Some case-control studies have found RRs among women that were nearly equal to (Schoenberg et al. 1989; Osann et al. 1993) or higher than those among men (Brownson et al. 1992b; Risch et al. 1993; Zang and Wynder 1996). A lower baseline risk for lung cancer or higher cigarette consumption among women smokers could explain the higher RR associated with ever smoking cigarettes among women (Hoover 1994; Wilcox 1994). In cohort studies, however, the death rates for lung cancer have been similar among women and men who had never smoked (Burns et al. 1997a; Thun et al. 1997a), and U.S. national survey data showed that the proportion of heavy smokers has consistently been higher over the years among men, not women (see Chapter 2). Several possible reasons may explain the higher smokingassociated RRs for lung cancer among women than among men reported from some case-control studies. The smoking patterns of women and men may differ in ways that have not been entirely accounted for in the study design and analysis. Women may under-report daily consumption of cigarettes and may, therefore, appear to have a higher risk than men for a given quantity smoked. Because smoking prevalence has always been higher among men than women (even though the gender gap has narrowed over time), women who smoke may also be more likely than men to be exposed to spousal smoking, which is itself associated with an increased risk for lung cancer (see "Environmental Tobacco Smoke" later in this chapter). Even when women smoke the same number of cigarettes as men do, exposure to cigarette smoke may be greater among women than among men because of differences in puff volume, puff frequency, or depth of inhalation. Alternately, women may be more biologically susceptible to the effects of cigarette smoke (Risch et al. 1993). McDuffie and colleagues (1991) observed that women with lung cancer developed disease at a younger age than did men and had a similar level of pulmonary dysfunction, but after less exposure to cigarette smoking. It is also likely that some of the observed gender differences represent chance findings. Thus, no conclusion regarding differential gender susceptibility to smoking-related lung cancer can be made at present.

Differences by gender in the proportion of lung cancer deaths directly attributable to current smoking are small. In CPS-II, the proportion of lung cancer deaths attributable to current smoking was 92 percent among women and 95 percent among men (Thun et al. 1997c). Smoking attributable fractions of deaths among women current smokers decreased with age, from 95 percent among women aged 45 through 49 years to 86 percent among women aged 80 years or older. This decrease among older women smokers likely is a result of differences in the smoking histories of older women, including later ages of initiation and lower cumulative exposures to smoking (Burns et al. 1997b). Nearly the same proportion of lung cancer deaths among women and men could be prevented by eliminating cigarette smoking.

Histologic Types

Lung cancers are classified into four main categories: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma (Churg 1994). Differences in histologic type have been observed between smokers and nonsmokers, and among smokers, gender-specific differences may be seen in the distribution of lung cancers by histologic type (Muscat and Wynder 1995b) (Table 3.9). In 1962, Kreyberg hypothesized that smoking causes squamous cell, small cell, and large cell carcinomas (Kreyberg type I), but that other factors cause adenocarcinoma and bronchioloalveolar carcinoma (Kreyberg type II) (Kreyberg 1962). Squamous cell carcinoma has long been the predominant type of lung cancer found among men, and adenocarcinoma has been predominant among women. Kreyberg (1962) based his hypothesis on this difference and on differences in the smoking habits of women and men at the time.

Although some early studies suggested that smoking might not be responsible for some histologic types of lung cancer, the association between smoking and all the major histologic types has been recognized since the 1980 Surgeon General's report (USDHHS 1980). Studies conducted since that report have confirmed that smoking strongly increases the risk for the four major types of lung cancer among women (Table 3.10). The risk was significantly higher among smokers than among women who had never smoked and, in general, increased as the quantity of cigarettes smoked increased (Lubin and Blot 1984; Wu et al. 1985; Schoenberg et al. 1989; Svensson et al. 1989; Katsouyanni et al. 1991; Morabia and Wynder 1991; Osann 1991; Brownson et al. 1992b; Osann et al. 1993; Zang and Wynder 1996) (Table 3.10). Risk also increased with duration of smoking (Schoenberg et al. 1989; Osann 1991; Risch et al. 1993) and depth of inhalation (Osann 1991) (data not shown). In one study, after adjustment for duration, risk did not increase with early age at smoking initiation for any histologic type of lung cancer (Svensson et al. 1989) (data not shown). Risk was generally lower among former smokers than among current smokers for each type of lung cancer (Wu et al. 1985; Svensson et al. 1989; Morabia and Wynder 1991; Osann 1991; Brownson et al. 1992b; Osann et al. 1993) (Table 3.10). Risk also decreased with duration of smoking cessation (Svensson et al. 1989; Morabia and Wynder 1991; Risch et al. 1993) (data not shown).

Among women, the RRs among smokers compared with those who had never smoked were consistently highest for small cell carcinoma (range, 37.6 to 86.0), followed by squamous cell carcinoma (range, 10.6 to 26.4), and then adenocarcinoma (range, 3.5 to 9.5) (Potter et al. 1985; Schoenberg et al. 1989; Brownson et al. 1992b; Osann et al. 1993; Risch et al. 1993) (Table 3.11). At each dose level of smoking, the RR was higher for small cell carcinoma than for squamous cell carcinoma and lowest for adenocarcinoma (Schoenberg et al. 1989; Brownson et al. 1992b; Osann et al. 1993; Zang and Wynder 1996) (data not shown). With the exception of the study by Risch and associates (1993), several investigators found that the risk among men was equally high for small cell and squamous cell carcinoma but lower for adenocarcinoma (Table 3.11). The RR among women and men who had ever smoked differed by less than a factor of 2 for adenocarcinoma (generally higher among men) and squamous cell carcinoma (higher among women in one-half of the studies), but the RR for small cell carcinoma among women consistently exceeded that among men by at least two to three times. In one study, dose-response RRs associated with specific levels of cumulative exposure to cigarette smoke (in kilograms of tar) were significantly higher by 1.5 to 1.7 times among women than among men for all three major histologic types (Zang and Wynder 1996).

Comparisons among histologic types and between women and men are subject to limitations because of diagnostic uncertainties, unstable estimates, and difficulties in assessment of cumulative exposure. Accurate classification of lung cancers into the four main histologic categories is compromised by interobserver variability and intrinsic tumor heterogeneity (Churg 1994). Comparisons of smoking-associated RR among histologic types and between genders are also limited by the small numbers of study participants who had never smoked. This limitation results in unstable risk estimates with wide, overlapping CIs. The lower smoking-associated risk for adenocarcinoma could be explained by a higher baseline risk for adenocarcinoma among women who had never smoked-a risk that is possibly due to exposure to ETS or other factors. Consistent with this explanation, adenocarcinoma does constitute a greater proportion of lung cancers among nonsmokers than among current or former smokers (Brownson et al. 1995; Muscat and Wynder 1995b). The subjective assessment of exposure to cigarette smoke may also differ between women and men.

Temporal Trends

Over time, the smoking habits of women have changed to more closely resemble those of men (Burns et al. 1997a). Differences between women and men in histologic patterns of lung cancer have lessened but have not disappeared (Wynder and Hoffman 1994).

The incidence of each of the main histologic types of lung cancer has increased among women since 1973, but adenocarcinoma had the greatest percent increase (206 percent during 1973-1992) (Surveillance, Epidemiology, and End Results Program, unpublished data) (Figure 3.8). Among men, the overall lung cancer rate has begun to decline, but adenocarcinoma increased by 84 percent during 1973-1992. The increasing incidence of adenocarcinoma among

both women and men may reflect the increase over time in the use of filter-tipped and low-tar cigarettes, which may result in greater deposition of smoke particles in the small airways of the lung periphery (Zheng et al. 1994). Yang and colleagues (1989) observed that smoke from filter-tipped and low-tar cigarettes contains fewer large particles and more small particles and may preferentially predispose smokers to peripheral tumors such as adenocarcinoma. Case-control results support an increased risk for adenocarcinoma among smokers of low-tar cigarettes (Stellman et al. 1997).

Analyses of gender-specific lung cancer trends by histologic type from data from the United States, Switzerland, and elsewhere showed that changes over time represent birth cohort effects reflecting gender-specific and generational changes in smoking and the types of cigarettes consumed (Levi et al. 1997; Thun et al. 1997b). For example, smoking among women was on the increase when filter-tipped and lower yield cigarettes were introduced. Such products are more likely to be inhaled than high-tar, unfiltered cigarettes because they are less irritating and because smokers compensate for the lower yield by smoking more intensely (greater number and depth of puffs). Thus, carcinogens may be more likely to travel beyond the central bronchi, where squamous cell carcinomas often occur, and to reach the bronchioloalveolar regions and smaller bronchi, where adenocarcinomas typically develop. Among women, the incidence of small cell carcinoma has increased steeply since 1973 and smaller increases have been seen in squamous cell carcinoma (Dodds et al. 1986; Wu et al. 1986; Butler et al. 1987; el-Torky et al. 1990; Devesa et al. 1991; Travis et al. 1995). An increase in bronchioloalveolar carcinoma found in hospital-based studies (Auerbach and Garfinkel 1991; Barsky et al. 1994) was not confirmed in population-based studies (Zheng et al. 1994). Analysis of more recent trends showed that rates for squamous cell carcinoma among women have remained fairly stable since the mid-1980s, rates for large cell carcinoma have decreased since the late 1980s, and rates for small cell carcinoma declined between 1991 and 1996. Incidence rates for adenocarcinoma, however, continued to increase, but the rate of increase appeared to be slowing (Wingo et al. 1999). Examination of trends by birth cohort revealed a decrease in the incidence of squamous cell carcinoma among birth cohorts of women and men born since 1935 and a reduction in the rate of increase in small cell carcinoma and adenocarcinoma among birth cohorts of women born since 1940 (Zheng et al. 1994).

Changes over time in the overall age-adjusted incidence of lung cancer can be primarily attributed to changes in smoking prevalence (Burns et al. 1997a). The steep rise in the incidence among women began in the 1960s and trailed the increase among men by about 20 years-a finding that reflects the later adoption of smoking by women. The recent decline in rates for squamous and small cell carcinomas and the slower rate of increase for adenocarcinoma among younger birth cohorts (Zheng et al. 1994) may be related to the decrease in smoking prevalence among these groups. Changes in smoking prevalence, however, may not explain all of the observed male-female differences in incidence patterns by histologic type. Additional risks related to use of low-tar, low-nicotine cigarettes and increasing exposure to tobacco-specific nitrosamines (TSNAs) may partially explain the increase in adenocarcinoma among women and men beginning in the 1970s (Wynder and Hoffman 1994).

Tobacco-Specific Nitrosamines

Wynder and Hoffman (1994) raised concerns about the level of TSNA carcinogens in brands of cigarettes smoked by women. The level of TSNA carcinogens in tobacco products is known to vary according to blend (Fischer et al. 1989), processing (Burton et al. 1989), and storage (Andersen et al. 1982c); this variation is a concern within the tobacco industry (Fisher 2000). As part of the validation of an analytical chemistry method to measure TSNAs in cigarette tobacco, the 10 best selling brands in the United States in 1996 were tested (Song and Ashley 1999). Two cigarettes from one pack of each brand were tested for this analysis. In this report, the 10 cigarette brands were ranked in the order of increasing *N*′-nitrosonornicotine (NNN) level, and Virginia Slims cigarettes (reported as Brand J in Table 5 in the report) (David Ashley, CDC, e-mail to Patricia Richter, CDC, August 31, 2000) were found to have the highest levels of NNN: 5.60 micrograms per gram (µg/g) of tobacco with a relative standard deviation of 1.4 percent, versus 1.89 µg/g with a relative standard deviation of 11 percent for Brand A. Of the TSNAs, NNN and *N*′-nitrosoanatabine

(NAT) levels correlated more closely; however, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosoanabasine (NAB) levels did not correlate with NNN or NAT levels across the 10 brands. Nevertheless, Virginia Slims had the highest levels of both NAB and NAT and the second-highest level of NNK. As alleged by a former Philip Morris chemist, internal industry testing of Virginia Slims cigarettes "found levels of nitrosamines 10 times higher than other cigarettes, including Marlboros" (Geyelin 1997). Although preliminary, these findings call for the rigorous testing of Virginia Slims and other cigarette brands popular among women who smoke.

Family History and Genetic Susceptibility Markers

Although approximately 90 percent of lung cancers are attributed to tobacco exposure, only a fraction of smokers (<20 percent) will develop lung cancer in their lifetime. Familial aggregation of lung cancer provides indirect evidence for a role of genetic predisposition to carcinogenesis from exposure to tobacco.

Lung cancer is prevalent in certain families (Lynch et al. 1978; Paul et al. 1987). In case-control studies, patients with lung cancer were more likely than control subjects to report having relatives with lung cancer (Lynch et al. 1986; Ooi et al. 1986; Samet et al. 1986; Sellers et al. 1987; Horwitz et al. 1988; Wu et al. 1988; Osann 1991; Shaw et al. 1991), and risk appears to increase with the number of first-degree relatives affected (Shaw et al. 1991). A study in Germany examined the effects of smoking and family history of lung cancer among case patients older than age 45 years and among those aged 55 through 69 years, and among control subjects of comparable age. After adjustment for pack-years of smoking, a first-degree family history of lung cancer was associated with a significantly increased risk for lung cancer among those in the younger age group (RR, 2.6; 95 percent CI, 1.1 to 6.0) but not the older age group (RR, 1.2; 95 percent CI, 0.9 to 1.6) (Kreuzer et al. 1998). Gender-specific results were not reported in that study, but the finding of a stronger association of family history with early onset of disease is consistent with an inherited predisposition. Another German case-control study, in which 83 percent of subjects were men, also found increased smoking-adjusted RRs associated with lung cancer in a parent or sibling, again with greater elevations in RR for cases diagnosed at younger (<51 years) relative to older ages (Bromen et al. 2000). Paternal but not maternal history of lung cancer was associated with increased risk. Elsewhere, smoking was found to interact synergistically with a family history of lung cancer and to increase lung cancer risk by 30 to 47 times the risk for nonsmokers with no family history of lung cancer (Tokuhata 1963; Horwitz et al. 1988; Osann 1991). In two studies, risk was greatest among female relatives (Ooi et al. 1986) and sisters of probands (McDuffie 1991). Findings from segregation analysis were compatible with Mendelian codominant inheritance of a rare major autosomal gene for predisposition to lung cancer. These findings also supported a model in which 62 percent of the population was susceptible and women were both more susceptible and affected at an earlier age than were men (Sellers et al. 1990).

These studies on patterns of inheritance suggested that a small proportion of lung cancer resulting from cigarette smoking is due to "lung cancer genes" that are likely to be of low frequency but high penetrance. The discovery of high-penetrance/low-frequency genes for lung cancer, however, is not likely to explain the vast majority of lung cancers. Instead, there may be low-penetrance genes of relatively high frequency that interact with smoking to increase the odds of developing lung cancer and for which attributable risks may be high. This field of investigation is burgeoning (Amos et al. 1992), but few definitive conclusions can be drawn as to which specific low-penetrance genes affect lung cancer risk or whether there are differential gender-specific effects.

Mutations in the p53 tumor-suppressor gene are more common in lung cancers among smokers than among nonsmokers, and the p53 mutational spectra differ between smokers and nonsmokers with lung cancer (Bennett et al. 1999; Gealy et al. 1999). The frequency of mutations correlates positively with lifetime exposure to cigarette smoking, and good evidence indicated that benzo[a'pyrene, a chemical carcinogen in cigarettes, causes specific p53 mutations (Bennett et al. 1999).

Future research in this area may identify smokers who, by virtue of their genetic profile, are at particularly high risk and may determine whether genderspecific differences exist in the effects of genetic susceptibility markers on the risk

for lung cancer associated with smoking. It is unlikely that one marker alone will be completely predictive of lung cancer risk; it is more likely that multiple susceptibility factors must be accounted for to represent the true dimensions of interactions between genes and exposure to tobacco.

Other Risk Factors

Cigarette smoking is overwhelmingly the most important cause of lung cancer. However, other risk factors that influence susceptibility to the effects of smoking have been identified (Kabat 1993; Ernster 1994); these include exposure to carcinogens such as radon and asbestos that act synergistically with cigarette smoking to increase lung cancer risk (Reif and Heeren 1999). Selected environmental exposures and host characteristics that may alter lung cancer risk in combination with cigarette smoking are discussed here.

Diet

The role of diet in the etiology of lung cancer has been reviewed and is supported by a large body of experimental and epidemiologic evidence (Goodman 1984; Colditz et al. 1987; Fontham 1990; Willett 1990). Both prospective studies (Hirayama 1984b; Steinmetz et al. 1993) and retrospective studies (Fontham et al. 1988; Koo 1988; Le Marchand et al. 1989; Jain et al. 1990) of women reported a 50-percent reduction in risk for lung cancer associated with high intake of fruits and vegetables containing beta-carotene. Although three studies found a significant protective effect of these dietary factors among women nonsmokers (Koo 1988; Kalandidi et al. 1990; Mayne et al. 1994), most studies included few nonsmokers and noted a protective effect primarily among smokers. This finding suggested a possible interaction of diet with smoking (Fontham 1990). No consensus has emerged about which group of smokers may enjoy the greatest protection-current smokers (Dorgan et al. 1993), heavy smokers (Dorgan et al. 1993), light smokers (Fontham et al. 1988; Le Marchand et al. 1989), or former smokers (Samet et al. 1985; Humble et al. 1987b; Steinmetz et al. 1993). Research has shown a reduced risk for squamous and small cell carcinomas, which occur predominantly among smokers, but has not shown a reduced risk for adenocarcinoma. These findings provided additional support for a possible interaction between smoking and consumption of carotenoids (Byers et al. 1987; Fontham et al. 1988). However, other studies reported significant inverse associations between carotenoids and adenocarcinoma (Wu et al. 1985, 1988; Koo 1988), large cell carcinoma (Steinmetz et al. 1993), and lung cancers of all cell types (Dorgan et al. 1993; Wu et al. 1994).

Despite the protective effects associated with fruits and vegetables in observational studies, largescale, randomized intervention trials showed either no benefit or a possibly harmful effect, at pharmacologic doses, of beta-carotene supplementation on lung cancer mortality, and no effect was found for alphatocopherol (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994; Omenn et al. 1996). Only one of the trials included women (Omenn et al. 1996).

Protective effects of preformed vitamin A (retinol) (Pastorino et al. 1987; Fontham et al. 1988; Koo 1988), vitamin C (Fontham et al. 1988; Koo 1988), vitamin E (Comstock et al. 1991; Mayne et al. 1994), and selenium (van den Brandt et al. 1993) were reported in some studies, but others reported no effect (Hinds et al. 1984; Samet et al. 1985; Wu et al. 1985, 1988; Byers et al. 1987; Humble et al. 1987b; Le Marchand et al. 1989). Epidemiologic studies of a possible increase in lung cancer risk with increased consumption of fat and cholesterol yielded conflicting results (Jain et al. 1990; Goodman et al. 1992; Alavanja et al. 1993; Wu et al. 1994). The ability to examine both independent associations and interactions of dietary factors with smoking is limited by small sample sizes and by inadequate estimation and analytic control for exposure to smoking.

Occupation

Few studies have examined specific occupational risks for lung cancer among women. Hazardous occupational exposures may explain 5 percent of lung cancers among women and 15 percent among men (Doll and Peto 1981).

Occupational studies are often subject to limitations because of an inadequate number of women and insufficient adjustment for the effects of cigarette smoking.

Regardless of limitations of studies, investigators have identified several occupational exposures that interact synergistically with smoking to increase risk beyond that observed for smoking alone (Ives et al. 1988; Saracci and Boffetta 1994). Results of combined analysis for Japanese women and men exposed to arsenic-contaminated drinking water supported a previously observed synergistic effect for smoking and arsenic exposure (Hertz-Picciotto et al. 1992; Tsuda et al. 1995).

Air Pollution

Although most cohort studies conducted in the 1950s through the 1970s that considered the effects of air pollution included only men, more recent case-control studies have included women and have attempted to control for smoking and other confounders. A case-control study in New Mexico found that living in urban areas was associated with increased smoking among non-Hispanic, white female controls; however, in multivariate analyses, living in urban areas was not associated with increased risk for lung cancer (Samet et al. 1987). Researchers also noted a significant association between smoking and duration of urban residence among women in the Niagara region of Ontario (Holowaty et al. 1991). However, even after adjustment for smoking, women in Shenyang, China, had a twofold increase in risk for lung cancer that was associated with living in a smoky environment, residing near industrial factories, and using coal-burning stoves (Xu et al. 1989). In Poland, researchers found interaction between the effects of smoking and air pollution among men but not among women (Jedrychowski et al. 1990). Among women in Athens, a nonsignificant interaction between the effects of smoking duration and air pollution was reported (Katsouyanni et al. 1991). Although data are potentially consistent with a small role for air pollution in lung cancer risk, the limitations of inadequate control of confounding from smoking and occupational exposures and the difficulties in measuring cumulative exposure preclude definite conclusions.

Radon and Ionizing Radiation

Radon gas is released from the decay of radium in rock, soil, and water, and it accumulates in mines, caves, and buildings. Findings in studies of uranium miners indicated that radon is a cause of lung cancer and suggested a synergistic effect with cigarette smoking (Samet 1989b; Samet et al. 1989; Lubin 1994; National Research Council 1999). Because women have traditionally spent more time in the home, they have a higher risk from exposure to residential radon than do men.

Results from studies of atomic bomb survivors, who are at increased risk for lung cancer, were consistent with either a multiplicative or additive relationship among radiation, smoking, and risk (Prentice et al. 1983). Elsewhere, an excess risk for developing lung cancer 10 or more years following radiotherapy for breast cancer was observed among women smokers (Neugut et al. 1994). Compared with nonsmokers who were not exposed to radiotherapy, study participants who were exposed to radiation alone had a RR of 3, those who smoked but were not exposed to radiation had a RR of 14, and those who both smoked and were exposed to radiation had a RR of nearly 33. Because no increased risk was found for the first 10 years after radiotherapy, some doubt exists about the causal nature of the association. Current radiotherapy practices deliver substantially less radiation to the lungs than previously and reduce any potential hazard.

Conclusions

1. Cigarette smoking is the major cause of lung cancer among women. About 90 percent of all lung cancer deaths among U.S. women smokers are attributable to smoking.
2. The risk for lung cancer increases with quantity, duration, and intensity of smoking. The risk for dying of lung cancer is 20 times higher among women who smoke two or more packs of cigarettes per day than among women

who do not smoke.

3. Lung cancer mortality rates among U.S. women have increased about 600 percent since 1950. In 1987, lung cancer surpassed breast cancer to become the leading cause of cancer death among U.S. women. Overall age-adjusted incidence rates for lung cancer among women appear to have peaked in the mid-1990s.
4. In the past, men who smoked appeared to have a higher relative risk for lung cancer than did women who smoked, but recent data suggest that such differences have narrowed considerably. Earlier findings largely reflect past gender-specific differences in duration and amount of cigarette smoking.
5. Former smokers have a lower risk for lung cancer than do current smokers, and risk declines with the number of years of smoking cessation.

International Trends in Lung Cancer Among Women

In 1990, cancers of the trachea, bronchus, and lung accounted for about 10 percent of all cancer deaths among women worldwide. The proportion of cancers varied widely among countries, which reflects the historical differences across countries in smoking initiation by women. Among women in Canada, the United Kingdom, and the United States, 20 percent or more of all cancer deaths were due to lung cancer; among women in France, Portugal, and Spain, the proportion was less than 5 percent. The estimated number of lung cancer deaths among women worldwide increased 23 percent between 1985 and 1990 (Pisani et al. 1999).

Since the early 1950s, lung cancer mortality for women in many industrialized countries has risen, on average, by more than 300 percent (Peto et al. 1994). Meanwhile, death rates among women for all other cancers combined have fallen by about 6 to 8 percent (Lopez 1995). Large prospective studies in the United Kingdom, the United States, and other industrialized countries showed that lung cancer death rates among nonsmokers have remained low, constant, and comparable among women and men (USDHHS 1989b; NCI 1997). These rates, about 5 cases per 100,000 persons (standardized to the European age structure of the World Health Organization [WHO]), are similar to the rates found for women in Southern Europe, where smoking prevalence among women has been low until recently.

Breast cancer has been the leading cause of cancer death among women in the industrialized world as a whole for about the last four decades. However, in some countries, notably Canada, Denmark, Scotland, and the United States, lung cancer now exceeds breast cancer as the principal cause of cancer death. Because lung cancer mortality is increasing among women in many countries, this crossover of death rates for the two cancer sites will probably occur in other countries as well. For women in the United States, the death rate for lung cancer also overtook the rate for colorectal cancer around 1980.

Trends in Developed Countries

The predominant determinant of the lung cancer trends among both women and men is cigarette smoking (Peto et al. 1994). Several decades elapse between the initiation of regular smoking by a particular generation and the manifestation of smoking-related lung cancer risk in that cohort (Doll and Peto 1981; Harris 1983; Brown and Kessler 1988). In the United States, for example, cigarette consumption among women did not substantially take hold until the 1930s and 1940s (USDHHS 1980) (see "Historical Trends in Smoking" in Chapter 2), and until the early 1960s, lung cancer death rates were low.

Data from the early 1990s indicated that Denmark (35.6 per 100,000 women) and the United States (36.9 per 100,000 women) had the highest lung cancer death rates. Australia, Canada, Hungary, New Zealand, England, Wales, and Ireland had rates around 20 to 30 deaths per 100,000 women (Table 3.12). These are some of the countries in which women first began cigarette smoking and in which the prevalence of smoking among women remained at a fairly high

level. Among developed countries, the lung cancer rates among women were lowest (about 10 cases or fewer per 100,000 women) in countries of Eastern and Southern Europe as well as in Finland and France.

The rate at which mortality from lung cancer has increased among women in different countries between 1985 and 1990-1993 is a public health concern (Table 3.12). Death rates rose most rapidly (about 5 percent per year) in Hungary, the Netherlands, and Switzerland; the percent increase was almost as high (3.3 to 3.7 percent per year) in several other countries, including Germany, Norway, and Sweden. Much more modest increases (about 0.5 percent per year) occurred in Bulgaria, Finland, Greece, Ireland, and Spain. In Ireland, the epidemic of lung cancer appears to have reached a plateau (Peto et al. 1994), but in Bulgaria, Finland, Greece, and Spain, low rates of increase suggested that the epidemic has yet to occur.

The range of lung cancer death rates in the early 1990s confirms that the lung cancer epidemic is heterogeneous even among women in industrialized countries (Peto et al. 1994). Countries for which data are available can be grouped into three broad categories describing trends of about the last four decades.

- Group 1: Countries where death rates are already high (about 20 deaths or more per 100,000 women) and, in most cases, are still rising or have peaked. These countries include Australia, Canada, Denmark, Hungary, Ireland, New Zealand, the United Kingdom, and the United States.
- Group 2: Countries where death rates are still moderately low (10 to 15 deaths per 100,000 women) but are rising. These countries include Austria, Germany, Italy, Japan, the Netherlands, Norway, Poland, Sweden, and Switzerland.
- Group 3: Countries where death rates are low (about 5 to 10 deaths per 100,000 women) and roughly stable and where the lung cancer epidemic generally has not yet become apparent among women. These countries include Bulgaria, Finland, France, Greece, Portugal, Romania, and Spain.

Although the countries in each group may have similar death rates at a given time, trends in rates over time may differ. For example, unlike some countries in Group 3, which has low rates, France and Portugal have rates that are low but have been rising since about 1980. Atrend of rising rates is evident in France, but it is not clear whether the increase in rates in Portugal is the beginning of an upward trend or a random fluctuation (Peto et al. 1994).

In the United Kingdom, the age-standardized lung cancer death rate among women has remained at around 31 deaths per 100,000 women since 1988. This rate, which is based on a large number of lung cancer deaths among women annually (about 12,500), suggested that the lung cancer epidemic has peaked among women in the United Kingdom. As noted earlier in this section, it also appears to have peaked in the United States (Wingo et al. 1999). The epidemic may have peaked in Australia, Ireland, and New Zealand, but because the number of lung cancer deaths in these countries is much smaller, the evidence is less conclusive.

Evidence that lung cancer rates among women in some areas may soon begin to rise was provided by trends in age-standardized death rates among women aged 35 through 54 years and among women aged 55 through 74 years. Lung cancer death rates among women aged 35 through 54 years have been declining since the late 1970s in the United Kingdom. Rates in this age group also appear to have reached their maximum level in Denmark and the United States more than a decade ago and more recently in Canada. On the other hand, rates among women aged 35 through 54 years were still rising in several countries in the early 1990s, for example in Hungary. The death rates among older women (aged 55 through 74 years) have generally continued to rise, as the cohorts most exposed to smoking have aged. However, death rates have already peaked and begun to decline among women in Ireland and the United Kingdom for this age group as well. The data for Australia and New Zealand also suggested that lung cancer mortality has peaked there among older women, but the trend is less conclusive in those two countries (Lopez 1995).

In several countries, including Austria, Germany, the Netherlands, Poland, Sweden, and Switzerland, and especially Hungary, the lung cancer death rate among women aged 35 through 54 years is relatively high compared with that

among women aged 55 through 74 years. The ratios of these rates suggested that the epidemic of lung cancer is beginning among younger middle-aged women who have now been smoking long enough to incur an increased risk for developing the disease. As these cohorts of women at high risk for disease grow older, the lung cancer epidemic among women is likely to continue to develop in those countries.

If the epidemic of lung cancer among women has peaked or will soon peak in those countries where it first began, then it will have been less severe than the epidemic among men (Peto et al. 1994). In the United Kingdom, the age-standardized lung cancer death rates among men peaked at 110 deaths per 100,000 men in the early 1970s. In the United States, the peak among men was lower-about 85 deaths per 100,000 men. If the circumstances in the United Kingdom and the United States are replicated in other countries, the lung cancer death rate among women may rise to only about one-third to one-half that found among men at the height of the epidemic of lung cancer among men.

Trends in Developing Countries

Mortality trends for lung cancer are not known for most developing countries, because data collection systems that would yield comparable, reliable estimates of mortality over time generally have not existed. However, current available data suggest that lung cancer death rates are generally low (Pisani et al. 1999), as would be expected for populations without a long history of smoking. An exception to the general pattern is the relatively high lung cancer rate among Chinese women in Asia (Parkin et al. 1999), despite the fact that relatively few Chinese women smoke. Factors other than smoking appear to be responsible for the high lung cancer death rates among women in China, possibly factors related to indoor air pollution created by certain cooking and heating sources. Despite the low prevalence of smoking, however, case-control studies have shown that smoking is also a strong risk factor for lung cancer among Chinese women (Wu-Williams et al. 1990).

Conclusion

1. International lung cancer death rates among women vary dramatically. This variation reflects historical differences in the adoption of cigarette smoking by women in different countries. In 1990, lung cancer accounted for about 10 percent of all cancer deaths among women worldwide and more than 20 percent of cancer deaths among women in some developed countries.

Female Cancers

Various factors associated with smoking, such as decreased fertility, age at menopause, and low body weight, are predictors of risk for many female cancers. The recognition that smoking can affect estrogenrelated diseases and events (Baron et al. 1990) provided further reason to examine the relationship between smoking and cancers influenced by endogenous hormones. Studies have also shown that smoking can influence the metabolism of exogenous hormones (Jensen et al. 1985; Cassidenti et al. 1990). These findings have prompted evaluation of combined effects of smoking and use of oral contraceptives (OCs) or menopausal estrogens, exposures that have been repeatedly examined with respect to various female cancers.

Breast Cancer

Indirect evidence suggests the biological possibility that smoking may reduce the risk for breast cancer. It is recognized that high levels of estrogens, particularly estrone and estradiol, contribute to an increased risk for breast cancer (Bernstein and Ross 1993), and smoking is thought to have an antiestrogenic effect (see "Sex Hormones" later in this chapter). The occurrence of menopause at an earlier age among smokers than among nonsmokers is also well established, and late age at menopause has been consistently related to an increased risk for breast cancer (Alexander and Roberts 1987). Thus, smoking could reduce the risk for breast cancer. On the other hand, cigarette smoke contains

numerous carcinogens that could plausibly affect the breast. Also, nicotine has been detected in the breast fluid of nonlactating women (Petrakis et al. 1978).

Multiple case-control studies and several cohort studies assessed the relationship between smoking and breast cancer risk (Palmer and Rosenberg 1993). The results of some studies, particularly hospital-based, case-control studies, must be interpreted cautiously. Smoking prevalence may be higher among hospital control subjects than among women in the general population and may result in an underestimation of the effects of smoking. Furthermore, questions have been raised about the results of some studies of women in breast cancer screening programs (Schechter et al. 1985; Meara et al. 1989) because the extent to which early detection methods are used may be correlated with smoking behaviors. Population-based studies are generally believed to provide the most valid results.

Many studies have reported no significant differences in breast cancer risk by whether participants had ever smoked (Rosenberg et al. 1984; Smith et al. 1984; Baron et al. 1986b, 1996b; Adami et al. 1988; Kato et al. 1989; London et al. 1989; Schechter et al. 1989; Ewertz 1990; Vatten and Kvinnsland 1990; Field et al. 1992; Braga et al. 1996; Engeland et al. 1996; Gammon et al. 1998; Millikan et al. 1998). (See Table 3.13 for results from case-control studies.) One study reported a lower but nonsignificant risk for breast cancer among current smokers but not among former smokers (O'Connell et al. 1987). Other studies reported a slightly to moderately higher risk among smokers (Schechter et al. 1985; Brinton et al. 1986b; Hiatt and Fireman 1986; Stockwell and Lyman 1987; Meara et al. 1989; Rohan and Baron 1989; Chu et al. 1990; Palmer et al. 1991; Bennicke et al. 1995; Morabia et al. 1996). Most elevations in RRs have been modest. Increased risk for breast cancer associated with smoking has been reported from at least two studies that used as the referent group women who were non-smokers and who had not been exposed to ETS (Lash and Aschengrau 1999; Johnson et al. 2000).

Most studies showed that RRs were generally similar for current and former smokers (Rosenberg et al. 1984; Lund 1985; Brinton et al. 1986b; Hiatt and Fireman 1986; London et al. 1989; Rohan and Baron 1989; Chu et al. 1990; Ewertz 1990; BaRon et al. 1996b; Braga et al. 1996). (See Table 3.13 for results from case-control studies.) In the few studies in which risk differed, the direction of the difference was inconsistent; some studies showed a higher risk among current smokers (Schechter et al. 1985; Stockwell and Lyman 1987; Brownson et al. 1988; Palmer et al. 1991), and other studies showed a higher risk among former smokers (Hiatt and Fireman 1986; O'Connell et al. 1987). Meara and colleagues (1989) showed a higher risk among current smokers aged 45 through 69 years in a screening program study and a decreased risk among current smokers aged 45 through 59 in a hospital-based study. One study showed an elevated risk among recent smokers that was restricted to postmenopausal women (Millikan et al. 1998). Similarly, studies that examined risk by years since smoking cessation or by age at cessation showed no substantive relationships (Chu et al. 1990; Field et al. 1992; BaRon et al. 1996b).

The majority of studies have indicated no differences in risk from either long-term or high-intensity smoking. Age at initiation of smoking also seems unrelated to breast cancer risk (Brinton et al. 1986b; Adami et al. 1988; Ewertz 1990; Palmer et al. 1991; Field et al. 1992; BaRon et al. 1996b; Braga et al. 1996). Furthermore, the few studies that examined risk by years since initiation of smoking showed no significant relationship (Adami et al. 1988; Braga et al. 1996). One study examined whether many years of smoking before a first-term pregnancy affected risk and found no adverse effect (Adami et al. 1988).

Some studies reported an increased risk for premenopausal breast cancer associated with ever smoking (Schechter et al. 1985), cigarette-years of smoking (Schechter et al. 1985), current but not former smoking (Brownson et al. 1988), or former smoking (Brinton et al. 1986b). Johnson and colleagues (2000) used never active smokers who had also not been exposed to ETS as the referent group and found that premenopausal women had an increased risk for breast cancer associated with active smoking and higher RRs than did postmenopausal women. In one study that focused on women whose breast cancers were detected before age 45 years, current smoking was related to reduced risk among women who began smoking before 16 years of age (Gammon et al. 1998). However, in another study, which included women with a diagnosis of breast cancer before age 36 years, smoking was not related to risk (Smith et al. 1994).

Most well-conducted studies have not confirmed an association between current or former smoking and premenopausal breast cancer (Hiatt and Fireman 1986; London et al. 1989; Rohan and Baron 1989; Schechter et al. 1989; Ewertz 1990; Field et al. 1992; BaRon et al. 1996b). In the large Cancer and Steroid Hormone (CASH) study in which only women younger than 55 years of age were included, Chu and associates (1990) found that smoking-associated risk for breast cancer was somewhat higher among women diagnosed before menopause; the differences by menopausal status at diagnosis were not statistically significant.

Smoking-associated risk was also examined by age at diagnosis of breast cancer, but again no definitive relationships were found. In the CASH study (Chu et al. 1990), risk was somewhat higher among women who had a diagnosis of breast cancer before age 45 years, but the interaction with age was not statistically significant. Stockwell and Lyman (1987) similarly found the highest risk when cancer was diagnosed before age 50 years, but Vatten and Kvinnsland (1990) reported no difference in the effects of smoking before and after age 51 years. In another study, women with a diagnosis of breast cancer at 65 years of age or older (Brinton et al. 1986b) had a smoking-associated RR less than 1.0. However, the data showed no trends in risk among current smokers with long duration or high intensity of smoking. Other investigators reported no substantial difference in risk for breast cancer among women by age at diagnosis (before or after age 50 years) (Palmer et al. 1991).

Although most studies did not find a significant relationship between smoking and breast cancer, the biological rationale for such a relationship has been compelling enough to motivate investigators to assess relationships within subgroups defined by hormonally related risk factors (e.g., use of exogenous hormones), hormone receptor status, and most recently, genetic polymorphisms.

Because evidence suggested that smoking might enhance the clearance of exogenous hormones, several studies evaluated whether any effects of smoking were modified by use of OCs or menopausal estrogens. In one study, cigarette smoking was strongly associated with breast cancer risk among women who had used either OCs or menopausal estrogens (Brinton et al. 1986b), but other studies failed to confirm this result (Adami et al. 1988; Chu et al. 1990; Ewertz 1990; Palmer et al. 1991; Gammon et al. 1998).

Most studies did not find the effects of smoking to be modified by additional risk factors, including parity, family history of breast cancer, body mass, alcohol consumption, dietary factors, and educational status (Rosenberg et al. 1984; Smith et al. 1984; Brinton et al. 1986b; Chu et al. 1990; Ewertz 1990; Palmer et al. 1991).

Data are conflicting on whether a different relationship might exist for smoking among estrogen receptor (ER)-positive tumors and among ER-negative tumors. In one population-based, case-control study, smoking was associated with a 63-percent higher risk for ER-negative tumors, a risk that was significantly different from the null association observed for ER-positive tumors (Cooper et al. 1989). This association of smoking with ER-negative tumors was confined to women with premenopausal cancer-an effect consistent with that found in a clinical study that included only women with breast cancer (Ranocchia et al. 1991). However, a second study reported the opposite relationship-a fairly weak association with smoking for women with ER-positive tumors (London et al. 1989). A third study found that the risks for both ER-positive and ER-negative breast cancer increased with both active and passive smoking (Morabia et al. 1998). Other studies have not shown cigarette smoking to vary by the ER status of tumors (McTiernan et al. 1986; Stanford et al. 1987b; Yoo et al. 1997).

ACS's CPS-II prospective study reported a significant increase in breast cancer mortality among current smokers (RR, 1.3); the risk from smoking for a long duration or at high intensity was even higher (RR, 1.7 for >40 cigarettes per day) (Calle et al. 1994). The investigators hypothesized that these findings could be due to delayed diagnosis of breast cancer among smokers or to a poorer prognosis among patients with breast cancer who smoke. Consistent with a poorer prognosis are results that showed a shorter average interval to recurrence of breast cancer among smokers than among nonsmokers (Daniell 1984) and poorer survival among patients with breast cancer who smoked than among nonsmokers (Yu et al. 1997). In another study, however, diagnosis of local breast cancer, as opposed to regional or distant breast cancer, was more likely among smokers than among nonsmokers (Smith et al. 1984). Thus, additional

studies are necessary to address how breast cancers are detected among smokers and how smoking affects the prognosis of the disease.

More recent studies focused on whether smoking may have unusual effects on breast cancer risk among genetically susceptible subgroups. These studies examined whether risk varied in the presence or absence of certain genetic polymorphisms involved in the activation or detoxification of carcinogens, including polymorphisms in *GSTM1*, *CYP1A1*, and *N*-acetyltransferase 2 (*NAT2*) genotypes. Although two studies did not find that the *GSTM1* genotype modified the effect of smoking on overall breast cancer risk (Ambrosone et al. 1996; Kelsey et al. 1997), one of the studies did find an increased risk for breast cancer among heavy smokers with specific polymorphisms in either the *CYP1A1* (Ambrosone et al. 1995) or *NAT2* genes (Ambrosone et al. 1996). Other studies have also identified some interaction of smoking with either the *NAT1*gene (Zheng et al. 1999), the *NAT2* gene (Morabia et al. 2000), or both genes (Millikan et al. 1998), but in the study of both genes, the effect was restricted to postmenopausal women who had smoked recently. Later data from the large prospective U.S. Nurses' Health Study did not find that the *NAT2* polymorphism increased the risk for breast cancer among smokers (Hunter et al. 1997), but did find some support for an interaction of smoking with the *CYP1A1* gene among women who began smoking early in life (Ishibe et al. 1998). Additional studies are examining potential interactions with these as well as other genetic polymorphisms. A recent study also suggested that cigarette smoking may reduce the risk for breast cancer among carriers of the highly penetrant genes *BRCA1* and *BRCA2* (Brunet et al. 1998). Studies are also beginning to assess the relationships between smoking and breast cancer within groups defined by tumor-suppressor genes; one recent investigation showed a higher risk associated with current cigarette smoking among patients with p53-positive tumors (Gammon et al. 1999). These various preliminary findings require further verification.

Correlations between the incidence of lung cancer among men and breast cancer among women in various countries and parts of the United States supported the hypothesis that ambient tobacco smoke may be related to breast cancer (Horton 1988). In a case-control study, exposure to ETS was associated with breast cancer among premenopausal women but not among postmenopausal women (Sandler et al. 1985, 1986), but the number of cases was small and the analysis was controlled only for age and level of education. In a large Japanese cohort study, Hirayama (1990) observed a significant dose-response relationship between the number of cigarettes smoked by husbands and their wives' risk for breast cancer at ages 50 through 59 years. In a case-control study of women younger than age 36 years, those exposed to ETS had an elevated risk for developing breast cancer, but the investigators noted little evidence of significant trends with increasing exposure (Smith et al. 1994).

Wells (1991, 1998) recommended further study of the effects of ETS exposure on breast cancer risk, because any risk associated with active smoking might be underestimated if the possibly confounding effect of ETS exposure is not considered. Indeed, the first study to examine this issue found a RR of 3.2 among nonsmoking women exposed to ETS compared with nonsmoking women who had not been exposed to ETS (Morabia et al. 1996). The plausibility of this finding was questionable because the RR associated with active smoking, using never active smokers as the referent group, was much higher (RR, 1.9 for smokers of >20 cigarettes per day) than that observed in other investigations. However, subsequent case-control studies that used persons who had never smoked or who had never been exposed to ETS as the referent group also found evidence of increased risk associated with ETS exposure (Lash and Aschengrau 1999; Johnson et al. 2000). In the study by Lash and Aschengrau (1999), the RRs associated with active smoking and with exposure to ETS were each 2.0, with evidence of higher risks among active smokers who smoked only before the first pregnancy and among subjects exposed to ETS before age 12 years. Similarly, in a large, population-based case-control study in Canada with adjustment for multiple potentially confounding variables, Johnson and colleagues (2000) found both ever active smoking and ETS exposure to be associated with increased risks for premenopausal and postmenopausal breast cancer after adjustment for multiple confounding variables. The referent group was women who were neither active smokers nor exposed to ETS. Millikan and associates (1998) reported positive associations between ETS exposure and breast cancer among never active smokers (RRs, 1.2 to 1.5), but the associations were weak and the findings were not statistically significant. In contrast, Wartenberg and

colleagues (2000) found no association between ETS exposure and breast cancer mortality in the CPS-II cohort study. They noted that after 12 years of follow-up, the risk was similar among women who were lifelong never smokers whose spouse was a current smoker at baseline and among women whose spouse had never smoked (multivariate RR, 1.0; 95 percent CI, 0.8 to 1.2), and no dose-response relationship was found. Biologically it is implausible that ETS exposure could impart a risk that is the same as that of active smoking, but whether ETS is related to breast cancer risk remains an open question and one that is receiving attention in other investigations.

The relationship of breast cancer risk to in utero exposure to tobacco smoke is also of interest because smoking may be associated with lower estrogen levels during pregnancy (Petridou et al. 1990). Although reduced estrogen levels might be expected to lower the risk for breast cancer, Sanderson and associates (1996), in a study that evaluated effects of maternal smoking and the risk for breast cancer, reported no significant effect overall and only a slight increase in risk among women diagnosed with breast cancer at age 30 years or younger whose mothers had smoked during pregnancy. This association persisted after the investigators considered the effects of birth weight.

Thus, active smoking does not appear to appreciably affect breast cancer risk overall. However, several issues are not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS exposure affects risk.

Benign Breast Disease

Studies provided mixed evidence as to whether smoking affects the risk for developing various benign breast conditions (Nomura et al. 1977; Berkowitz et al. 1985; Pastides et al. 1987; Rohan et al. 1989; Parazzini et al. 1991b; Yu et al. 1992). To compare the results of these studies is difficult because they differ by the types of conditions examined (fibroadenoma, fibrocystic disease, or proliferative disorders of varying degrees of severity), by how smoking status was defined (ever, current, or former smoking), and by whether data were analyzed by menopausal status.

Endometrial Cancer

Some researchers proposed that exposure to tobacco may reduce the risk for endometrial cancer by reducing estrogen production (MacMahon et al. 1982), a hypothesis that received some support from findings that estriol excretion is reduced among postmenopausal smokers (Key et al. 1996). Another theory is that smoking affects endometrial cancer risk by altering the metabolism, absorption, or distribution of hormones. Research has shown that smokers have higher rates of conversion of estradiol to 2-hydroxyestrones, which have low estrogenic activity (Michnovicz et al. 1986). Furthermore, antiestrogenic effects of smoking may be mediated by inducing microsomal, mixed-function oxidase systems that metabolize sex hormones (Lu et al. 1972). Both mechanisms are consistent with findings that women smokers who take oral estradiol have lower levels of unbound estradiol and higher serum hormone-binding capacity than do women nonsmokers who take estradiol (Jensen et al. 1985; Cassidenti et al. 1990). However, other mechanisms should not be dismissed. For example, several investigators believe that the effects of smoking on androgen, progestogen, or cortisol may reduce the risk for endometrial cancer among smokers (Seyler et al. 1986; Khaw et al. 1988; Baron et al. 1990; Berta et al. 1991).

Multiple case-control studies showed a reduced risk for endometrial cancer among cigarette smokers (Baron et al. 1986b; Franks et al. 1987a; Levi et al. 1987; Stockwell and Lyman 1987; Kato et al. 1989; Koumantaki et al. 1989; Dahlgren et al. 1991; Brinton et al. 1993; Parazzini et al. 1995) (Table 3.14). Several other studies found reduced risks among smokers that were not statistically significant (Smith et al. 1984; Lesko et al. 1985; Tyler et al. 1985; Lawrence et al. 1987; Weir et al. 1994). Some of these studies examined results by menopausal status and showed that the reduced risk among smokers was restricted to women with endometrial cancer diagnosed after menopause (Lesko et al. 1985; Stockwell and Lyman 1987; Koumantaki et al. 1989; Parazzini et al. 1995). Among postmenopausal women, the magnitude of the risk reduction associated with ever smoking was about 50 percent. One study found a

significantly elevated risk for premenopausal endometrial cancer associated with ever smoking (Smith et al. 1984). In most studies that showed a reduced risk associated with smoking, the effect was greater among current smokers than among former smokers or was confined to current smokers.

The factors that are known to increase the risk for endometrial cancer and that are potential confounders of the association between smoking and the disease include obesity, late onset of menopause, menstrual disorders, infertility, and use of menopausal estrogens; reduced risk has been associated with use of OCs. Despite careful control for these variables, the magnitude of observed reductions in risk associated with smoking has not been substantially affected.

Beside considering confounding effects, several investigators assessed whether the presence of selected risk factors could modify the relationship between smoking and endometrial cancer risk. Three studies noted a greater reduction in smoking-associated risk among obese women (Lawrence et al. 1987; Brinton et al. 1993; Parazzini et al. 1995). Other research indicated that obesity enhances the capacity to produce estrogens through extraovarian sources and is associated with higher levels of sex hormone-binding globulin (Siiteri 1987). Several studies reported a greater reduction in risk for smokers than nonsmokers among women taking estrogen replacement therapy (Weiss et al. 1980; Franks et al. 1987a), but not all study results supported such an effect (Brinton et al. 1993; Parazzini et al. 1995). One study found the greatest reduction in risk associated with smoking among multiparous women (Brinton et al. 1993).

Endometrial hyperplasia is generally recognized as a precursor of endometrial cancer (Kurman et al. 1985). Weir and colleagues (1994) examined the association between smoking and endometrial hyperplasia and showed a lower RR among both premenopausal and postmenopausal women smokers. The results of this study, however, were not statistically significant.

Ovarian Cancer

Frequency of ovulation has been hypothesized in regard to risk for epithelial ovarian cancer: the greater the number of ovulatory cycles in a lifetime, the greater the risk (Whittemore et al. 1992). If smoking interrupts ovulation, as suggested by menstrual irregularity and subfecundity among smokers (see "Menstrual Function" and "Reproductive Outcomes" later in this chapter), smoking could lower the risk for ovarian cancer. On the other hand, cigarette smoke contains carcinogens, which could increase the risk for ovarian cancer. Furthermore, enzymes in the ovaries of rodents have been shown to metabolize polycyclic aromatic hydrocarbons (PAHs) to electrophilic intermediates, and exposure to these compounds through smoking may have direct toxic effects or may stimulate ovarian atresia (imperforation or closure). Thus, the risk for ovarian cancer may be increased (Mattison and Thorgeirsson 1978). A broad range of possible biological effects of smoking on ovarian tissue or on hormones exists, but studies have not examined the relationship of smoking with risk for ovarian cancer in detail. In most studies in which the effects of smoking were evaluated, only limited information on exposure was collected, and comparisons were usually dependent on hospital-based control subjects. In fact, few studies have considered the combined influence of smoking and other risk factors for ovarian cancer. Further research is also needed on the relationship of smoking with histologic subtypes of ovarian cancer.

Most investigations of the relationship between the risk for ovarian cancer and a history of ever having smoked have found no association (Byers et al. 1983; Smith et al. 1984; Baron et al. 1986b; Franks et al. 1987b; Stockwell and Lyman 1987; Hartge et al. 1989; Kato et al. 1989; Hirayama 1990; Polychronopoulou et al. 1993; Engeland et al. 1996; Mink et al. 1996). Table 3.15 shows results of case-control studies that provided estimates of RR.

Only a few studies examined the relationship of ovarian cancer with duration or intensity of smoking. Astudy in Greece found a slightly reduced risk among smokers who smoked 20 or more cigarettes per day, but the relationship was not statistically significant (Tzonou et al. 1984). The CASH study reported that risk for ovarian cancer did not vary in relation to quantity of cigarettes smoked and duration of smoking, including the interval since smoking cessation, the number of pack-years of smoking, the interval since initiation of smoking, and age at initiation (Franks et al. 1987b). Furthermore, smoking effects did not vary by several other factors, including reproductive history,

menopausal status, use of exogenous hormones, alcohol use, and family history of ovarian cancer. However, the CASH study included only women with a diagnosis of ovarian cancer before age 55 years, which limits the generalizability of the results. Studies that included a broader age range of women found no substantial relationship of ovarian cancer risk with current smoking or duration of smoking (Stockwell and Lyman 1987; Hartge et al. 1989).

Cervical Cancer

Apositive correlation between the incidence of cervical cancer and other cancers known to be related to cigarette smoking across populations prompted the hypothesis that smoking may affect the risk for cervical cancer (Winkelstein 1977). Excess risk for cervical cancer among smokers was demonstrated in a number of case-control studies (Clarke et al. 1982; Marshall et al. 1983; Baron et al. 1986b; Brinton et al. 1986a; La Vecchia et al. 1986; Peters et al. 1986; Nischan et al. 1988; Licciardone et al. 1989; Bosch et al. 1992; Daling et al. 1996). (See Table 3.16 for studies that provided data on smokers and never smokers.) One cohort study also found an excess risk for cervical cancer among smokers (Greenberg et al. 1985). In these studies, the association between cervical cancer and smoking was not eliminated, even though the investigators controlled for several well-established risk factors for cervical cancer, including early age at first sexual intercourse, history of multiple sex partners, and low socioeconomic status.

Several subtypes of human papillomavirus (HPV) are recognized as the main cause of cervical cancer worldwide (Bosch et al. 1995), and the extent to which the relationship between smoking and cervical cancer reflects a causal association independent of HPV infection is not known. The association of smoking with cervical cancer may be causal, may reflect confounding or risk modification among women with HPV infection, or may even reflect an effect of smoking on risk for HPV infection. Residual confounding by sexual history may also explain observed smoking associations, and adjustment for HPV will probably address that possibility.

Most studies in which risk values were not adjusted for HPV infection reported a RR of approximately 2.0 among smokers compared with nonsmokers. Women who smoked for a long duration or at high intensity generally had the highest risk (Table 3.16). In several studies, the relationship was restricted to, or strongest among, recent or current smokers (Brinton et al. 1986a; La Vecchia et al. 1986; Licciardone et al. 1989). Two studies reported the highest risk among women who started smoking late in life (Brinton et al. 1986a; Herrero et al. 1989), but other studies reported the opposite effect, namely higher risk among women who began smoking at young ages (La Vecchia et al. 1986; Daling et al. 1996). The results from several studies showed further biological evidence to support an association between cervical cancer and smoking. The findings included an enhanced risk associated with continuous smoking (Slattery et al. 1989), use of unfiltered cigarettes (Brinton et al. 1986a), and inhaling smoke into the throat and mouth (Slattery et al. 1989). The effects of smoking appear to be restricted to squamous cell carcinoma; no relationship was observed for the rarer occurrences of adenocarcinoma or adenosquamous carcinoma (Brinton et al. 1986a).

In numerous studies, an association with smoking appears to prevail for both cervical cancer and precursor conditions, including carcinoma in situ and cervical dysplasia (also known as squamous intraepithelial neoplasia) (Harris et al. 1980; Berggren and Sjostedt 1983; Hellberg et al. 1983; Lyon et al. 1983; Trevathan et al. 1983; Clarke et al. 1985; Mayberry 1985; La Vecchia et al. 1986; Brock et al. 1989; Slattery et al. 1989; Coker et al. 1992; Gram et al. 1992; Parazzini et al. 1992a; Munoz et al. 1993; Becker et al. 1994; de Vet et al. 1994; Kjaer et al. 1996; Ylitalo et al. 1999) (Table 3.17). Most of these studies reported particularly high risk among current smokers and among those who smoked for a long time or at a high intensity, but they have been limited by the absence of information on HPV. In one study, smoking did not affect the overall risk for cervical intraepithelial neoplasia (CIN) when sexual history and HPV infection status were taken into account (Schiffman et al. 1993). However, current cigarette smoking was related to nearly a threefold increase in risk among the limited number of HPV-positive women who had a higher grade of disease (CIN II or III). Elsewhere, in a clinics-based study among HPV-infected women in which women with CIN I served as the referent group, smoking was significantly associated with CIN III (Ho et al. 1998). These findings suggested that smoking may be involved in disease progression. They were supported by results in two other studies

that were limited by the absence of data on HPV status. In those studies, smoking was a risk factor only for CIN III (Coker et al. 1992) or was a stronger risk factor for CIN III than for CIN II (Trevathan et al. 1983).

Investigators in only a few studies evaluated the interaction between smoking and other risk factors for cervical cancer. One study found no significant variation by other factors, including sexual behavior and history of sexually transmitted disease (STD) (Mayberry 1985). Two studies reported that the effects of smoking were greatest among women with a history of limited sexual activity (Nischan et al. 1988; Slattery et al. 1989). However, in another study, the effects of smoking were greatest among women who were married multiple times or who had more than one sexual partner (La Vecchia et al. 1986). Lyon and associates (1983) found the effects of smoking to be greater among Mormon women, who tend to begin to bear children at a younger age than do other women in the United States.

Because HPV infection, which is usually contracted from a sexual partner, is widely recognized as the main cause of cervical cancer, Phillips and Smith (1994) focused on ways to assess whether the association between smoking and cervical cancer is independent of HPV infection. HPV occurs frequently among women with cervical cancer but infrequently in control subjects. Thus, recent studies have examined smoking effects by status of HPV infection among subgroups of women. An early study found the effects of smoking to be most pronounced among women infected with HPV, but these results may have been limited by imprecise assays to detect HPV (Herrero et al. 1989). Several studies using reliable measures of HPV reported that smoking was not associated with risk for cervical cancer among HPV-positive women (Bosch et al. 1992; Munoz et al. 1993; Eluf-Neto et al. 1994). This finding suggested that cigarette smoking may not affect risk for cervical cancer independently of HPV infection status. However, all these studies were conducted in Latin America, where the effects of smoking on cervical cancer have been found to be weak-possibly because few women in these studies have a history of smoking for a long duration or at a high intensity (Herrero et al. 1989). Thus, it is noteworthy that two studies, one in the United States and the other in Denmark, found smoking to be a risk factor among both HPV-positive and HPV-negative women (Daling et al. 1996; Ylitalo et al. 1999).

Several research teams have attempted to define possible mechanisms by which smoking might alter the cervical epithelium. Because of the high levels of nicotine and cotinine detected in the cervical mucus of smokers, the researchers initially investigated a direct effect of smoking (Sasson et al. 1985; Schiffman et al. 1987; McCann et al. 1992). Zur Hausen (1982) also suggested that the oncogenicity of HPV may be enhanced by certain chemical compounds, including those in tobacco smoke. The results of one study supported this hypothesis (Herrero et al. 1989), but others did not find an enhanced effect of smoking among HPV-positive women (Munoz et al. 1993; Eluf-Neto et al. 1994). More recent studies reported no significant difference in smoking-related DNA damage (DNA adduct levels) in the cervical epithelium of HPV-positive and HPV-negative smokers (Simons et al. 1995). Attention also focused on whether smoking might cause local immunosuppression within the cervix as a result of a decrease in the number of Langerhans' cells (Barton et al. 1988). Some have suggested that such immunosuppression may allow the persistence of HPV. For example, one study showed that the prevalence of HPV was positively associated with the number of cigarettes smoked per day (Burger et al. 1993). Hildesheim and colleagues (1993), however, did not find smoking to be strongly associated with the risk for cervical HPV infection, when correlations with sexual behavior were taken into account. Thus, whether the relationship between smoking and cervical cancer is biological or reflects residual confounding remains unclear.

Further clues to mechanisms of the effects of smoking may be revealed by examining interaction with dietary factors. Several investigators suggested that diets low in carotenoids or vitamin C may predispose women to cervical cancer (Brock et al. 1988; La Vecchia et al. 1988; Verreault et al. 1989). The results of one study suggested that the effects of cigarette smoking were more pronounced among women with high levels of antioxidants than among those with low levels, but these findings were not statistically significant (Brock et al. 1989). Because smokers may have lower levels of plasma beta-carotene than do nonsmokers (Brock et al. 1988) and because nutrition may affect the persistence of HPV (Potischman and Brinton 1996), studies that focus on the combined effects of cigarette smoking, nutrition, and HPV persistence may prove insightful.

The effects of exposure to ETS on risk for cervical cancer began to receive attention in the 1980s. Investigators addressed these effects primarily by studying the smoking behavior of partners of women or by directly questioning women about their passive exposure to cigarette smoke. Two studies that focused on husbands found that the prevalence of smoking was higher among husbands of women with cervical cancer than among husbands of control subjects (Buckley et al. 1981; Zunzunegui et al. 1986). However, Buckley and colleagues (1981) accounted for the number of sexual partners of the husbands and found that ETS exposure did not persist as a significant predictor of risk. In a study of intraepithelial neoplasia, Coker and colleagues (1992) found no consistent association with ETS exposure. On the other hand, Slattery and associates (1989) found that women with passive exposure to cigarette smoke for three or more hours per day had nearly a threefold increase in risk. In fact, the effect was even more enhanced for women nonsmokers. Additional studies are needed to determine whether ETS exposure actually increases risk for cervical cancer or whether it appears to do so because of confounding factors that have not been adequately controlled in some of the studies to date. McCann and associates (1992) examined nicotine and cotinine levels in cervical mucus and found no real differences between nonsmoking women who did or did not report exposure to ETS.

Vulvar Cancer

In several studies, the risk for cancer of the vulva has been higher among smokers than among non-smokers (Newcomb et al. 1984; Mabuchi et al. 1985; Brinton et al. 1990). In one investigation, the risk was about twice as high among current smokers than among nonsmokers or former smokers and even higher among current smokers who had smoked at a high intensity (Brinton et al. 1990). The increased risk among current smokers, which was also reported for cervical cancer, is consistent with the action of cigarette smoke as a promoter in the late stages of carcinogenesis.

Results from all studies were limited by the absence of reliable information on the status of HPV infection, which is an accepted risk factor for vulvar cancer (Andersen et al. 1991). Because the risk for vulvar cancer is higher among smokers with a history of condylomata or genital warts, which are caused by HPV infection (Brinton et al. 1990), future studies should address whether data on the effects of smoking are confounded by HPV infection status and whether risk is modified by the presence of HPV. Findings from several small clinical studies (Andersen et al. 1991; Bloss et al. 1991) supported the hypothesis that smoking may predispose women to the subset of vulvar cancers most strongly linked with HPV infection-cancers with intraepithelial-like growth patterns-rather than the well-differentiated vulvar cancers more common among older women. Zur Hausen (1982) proposed that the effect of HPV infection may be enhanced by other risk factors. Immune alterations are a plausible mechanism for this synergistic relationship. Smoking has been linked with several changes in immune function (Hughes et al. 1985; Barton et al. 1988), and HPV infection occurs more commonly among persons with immunosuppression (Sillman et al. 1984).

Conclusions

1. The totality of the evidence does not support an association between smoking and risk for breast cancer.
2. Several studies suggest that exposure to environmental tobacco smoke is associated with an increased risk for breast cancer, but this association remains uncertain.
3. Current smoking is associated with a reduced risk for endometrial cancer, but the effect is probably limited to postmenopausal disease. The risk for this cancer among former smokers generally appears more similar to that of women who have never smoked.
4. Smoking does not appear to be associated with risk for ovarian cancer.
5. Smoking has been consistently associated with an increased risk for cervical cancer. The extent to which this association is independent of human papillomavirus infection is uncertain.

6. Smoking may be associated with an increased risk for vulvar cancer, but the extent to which the association is independent of human papillomavirus infection is uncertain.

Other Cancers

Smoking has been shown to increase the risk for cancer at sites outside the respiratory system, including the digestive system, the urinary tract, and the hematopoietic system. Previously, information on the effects of smoking was derived primarily from epidemiologic studies of men (USDHHS 1989b), but later data from studies of women showed generally similar patterns of risk for equivalent levels of exposure.

Oral and Pharyngeal Cancers

Numerous cohort and case-control studies have shown that the main risk factors for cancers of the mouth and pharynx are smoking and alcohol use (Blot et al. 1996). These associations hold for cancers of the mouth, tongue, and pharynx, almost all of which are squamous cell carcinomas, but little or no association has been shown for salivary gland tumors, which are extremely rare and are generally adenocarcinomas (Preston-Martin et al. 1988; Horn-Ross et al. 1997).

In almost all populations, oral and pharyngeal cancers occur more frequently among men than among women (Parkin et al. 1992). However, smoking increases the risk for these cancers among both genders. In CPS-II, the risk for death from oral or pharyngeal cancer was five times higher among women current smokers than among women who had never smoked (Table 3.18). In a cohort study from Sweden, women who smoked also had an increased risk for oropharyngeal cancer incidence (Nordlund et al. 1997).

In a large, population-based case-control study that included more than 350 women with cancer, the risk for oral or pharyngeal cancer rose progressively with the duration of smoking and the number of cigarettes smoked. After adjustment for alcohol intake, the risk for oral and pharyngeal cancers was 10 times greater among women who were long-term (> 20 years), heavy (>2 packs per day) smokers than among women nonsmokers. Smoking cigarettes and drinking alcohol in combination greatly increased risk. The risk for these cancers was more than 10 times greater among women who had 15 or more drinks a week and smoked 20 or more cigarettes a day for 20 or more years than among women nonsmokers and nondrinkers (Blot et al. 1988). These high RRs may exceed those among men (Blot et al. 1988; Kabat et al. 1994b; Macfarlane et al. 1995; Muscat et al. 1996; Talamini et al. 1998). Among both women and men, the risk for these cancers does not appear to be elevated among persons who had stopped smoking for 10 or more years (Blot et al. 1988; Kabat et al. 1994b; Macfarlane et al. 1995). This rapid reduction in risk suggested that smoking affects a late stage in the process of oral and pharyngeal carcinogenesis and that women can substantially decrease their risk in a fairly short time if they stop smoking. About 60 percent of oral and pharyngeal cancers among women are due to the combined effects of tobacco and alcohol (Blot et al. 1988; Negri et al. 1993), but smoking-related risk for oral and pharyngeal cancer exists even among women who do not drink alcohol (Macfarlane et al. 1995; La Vecchia et al. 1999).

Use of smokeless tobacco also increases the risk for oral cancer, particularly at sites that have direct contact with the tobacco product. This finding has been reported in India and other Asian countries, where use of smokeless tobacco is common (International Agency for Research on Cancer [IARC] 1985; USDHHS 1986a; Nandakumar et al. 1990; Sankaranarayanan 1989a, b, 1990), but evidence also comes from studies of women in rural areas of the southern United States. In a study of women in North Carolina (Winn et al. 1981), the RR for cancers of the cheek and gum rose sharply with use of snuff. Among women who had used snuff for 50 or more years, the risk for oral cancer was 50 times that among women who had not used snuff. Indeed, in this population, nearly all cancers of the gum and buccal mucosa were attributable to long-term use of snuff.

Laryngeal Cancer

Laryngeal cancer is a relatively rare disease among women; the male-to-female incidence ratio is 5:1. Survival is relatively good; about 70 percent of patients live 5 or more years after diagnosis (Austin and Reynolds 1996). This cancer is caused largely by heavy smoking and heavy drinking of alcohol (Tavani et al. 1994a; Austin and Reynolds 1996). Data are limited on the relationship between cigarette smoking and laryngeal cancer among women, but these data also showed a much higher risk among smokers than among persons who had never smoked. In CPS-II, the risk for death from laryngeal cancer among women current smokers was 13 times that among women who had never smoked (Table 3.18). Similarly, in a multisite case-control study, Williams and Horm (1977) reported a risk ratio of 17.7 for laryngeal cancer among women who had smoked more than 40 pack-years compared with women nonsmokers. In another case-control study, Wynder and Stellman (1977) found a RR of 9.0 among women who were long-term smokers (>40 years). Case-control studies from Italy and China reported even higher RRs (Zheng et al. 1992; Tavani et al. 1994a). Although the reported RR estimates were based on small numbers of subjects and consequently were not precise, they are compatible with a 10-fold higher risk among current smokers than among nonsmokers. Studies conducted largely among men indicated that smoking cessation decreases the smoking-related risks (Tuyns et al. 1988; Falk et al. 1989).

Esophageal Cancer

Esophageal cancer is also a malignant disease that occurs among men much more often than among women (Parkin et al. 1992). The high male-to-female incidence ratio applies to both squamous cell carcinoma, the most common histologic type of esophageal cancer in most populations, and adenocarcinoma, a cell type rapidly rising in incidence in the United States and parts of Europe (Blot et al. 1991). Smoking, combined with drinking alcohol, has consistently been shown to be a strong risk factor for squamous cell esophageal cancer and appears to increase the risk for adenocarcinoma (Blot 1994; Brown et al. 1994b; Vaughan et al. 1995; Gammon et al. 1997).

Only limited data are available on the effect of smoking on the risk for esophageal cancer among women, but no evidence suggests that these effects differ among women and men. In an investigation of esophageal cancer among women in northern Italy, smoking was the main risk factor and risk increased with the amount smoked; women who smoked one or more packs of cigarettes per day had five times the risk of nonsmokers (Negri et al. 1992; Tavani et al. 1993). Among women in CPS-II, the risk for death from esophageal cancer among current smokers was almost eight times higher than that among women who had never smoked (Table 3.18). Studies of smoking cessation, largely among men, have consistently found excess risk to be reduced, but not eliminated, after cessation (IARC 1986; USDHHS 1989b; Tavani et al. 1993).

Stomach Cancer

Smoking may increase the risk for stomach cancer (McLaughlin et al. 1990; Kneller et al. 1991; Hansson et al. 1994; Nomura 1996; Trédaniel et al. 1997), but some investigators have shown no association (Buiatti et al. 1989; Trédaniel et al. 1997). The excess risks reported have been smaller than those found for oral or esophageal cancer, and dose-response trends have been absent or relatively weak. Nonetheless, differences in diet between smokers and nonsmokers do not appear to totally explain the difference in risk (Hansson et al. 1994).

Among women participating in CPS-II, the risk for mortality from stomach cancer was 40 percent higher among current smokers and former smokers than among never smokers (Table 3.18). These findings are consistent with the evidence among men (McLaughlin et al. 1995a). In several case-control studies, differences by gender in smoking-related risks were small (Haenszel et al. 1972; Kono et al. 1988; Kato et al. 1990; Tominaga et al. 1991; Burns and Swanson 1995; Chow et al. 1999), but several investigators found indications of a weaker effect among women (Trédaniel et al. 1997; Inoue et al. 1999). In both cohort studies (USDHHS 1989b; McLaughlin et al. 1995b) and case-control studies (Hansson et al. 1994), risk for stomach cancer among former smokers was not significantly elevated compared with persons who had never smoked. Subjects in these studies were mostly men.

Colorectal Cancer

Smoking has been associated with a twofold to threefold excess risk for colorectal adenomas, benign precursors of most colorectal cancers (Kikendall et al. 1989; Lee et al. 1993; Neugut et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994a; Newcomb et al. 1995), but its association with colorectal cancer has been more controversial (Kune et al. 1992; Terry and Neugut 1998). Several cohort and case-control studies of women found no excess risk for colon or rectal cancer among smokers (Sandler et al. 1988; Akiba and Hirayama 1990; Chute et al. 1991; Kune et al. 1992; Baron et al. 1994b; Boutron et al. 1995; D'Avanzo et al. 1995a; Engeland et al. 1996; Nordlund et al. 1997; Knekt et al. 1998). However, CPS-II found small increases in the risk for death from cancers of the colon (RR, 1.3) and rectum (RR, 1.4) among women current smokers on the basis of 6 years of follow-up (Table 3.18). A more detailed analysis after 14 years of follow-up of the CPS-II cohort found that, in general, risk for colorectal cancer death increased with the number of cigarettes smoked and with pack-years of smoking (Chao et al. 2000). Moreover, some cohort studies that had 20 years or more of follow-up showed a moderately elevated risk for colorectal cancer death among smokers, for both women (Doll et al. 1980) and men (Doll et al. 1994; Heineman et al. 1994). In a pair of related cohort studies (Giovannucci et al. 1994a, b), smoking was associated with an increased risk for developing colorectal cancer after a latent period of 35 years among both women and men. Risk for colorectal cancer also has been modestly associated with cigarette smoking in some case-control studies of women (Newcomb et al. 1995; Le Marchand et al. 1997; Slattery et al. 1997). In some analyses, excess risks for long-term smokers were not reduced substantially after smoking cessation (Chute et al. 1991; Heineman et al. 1994; Newcomb et al. 1995). Several other studies of women found smoking-related RRs to be greater for cancer of the rectum than for cancer of the colon (Doll et al. 1980; Inoue et al. 1995; Newcomb et al. 1995).

Liver and Biliary Tract Cancers

Heavy alcohol use and chronic hepatitis B infection are recognized risk factors for hepatocellular carcinoma (IARC 1988), but the role of cigarette smoking is less clear. An early study reported an increased risk for hepatocellular carcinoma, even after adjustment for alcohol intake, among women and men smokers who did not have hepatitis B infection (Trichopoulos et al. 1980). Among the women in CPS-II, the mortality rate for liver cancer was 60 percent higher among current smokers than among those who had never smoked (Table 3.18). In the studies that presented data separately for women (Table 3.19), the RR estimates for liver cancer were generally similar to those among men and ranged from no association (Stemhagen et al. 1983) to a threefold excess risk among current smokers (Tsukuma et al. 1990). Risk for liver cancer rose with increasing number of cigarettes smoked per day in some studies (Yu et al. 1988, 1991) but not in others (Stemhagen et al. 1983; Tsukuma et al. 1990; Goodman et al. 1995; Tanaka et al. 1995). Smoking cessation has typically been associated with a modest reduction in the RR for liver cancer, particularly after sustained cessation (Yu et al. 1988, 1991; Tsukuma et al. 1990; Goodman et al. 1995), but among women in CPS-II, the RR for death from liver cancer among former smokers was not reduced (Tables 3.18 and 3.19). Thus, smoking may be a contributing factor in the development of liver cancer, but further clarification of the effect among women is needed.

Cancers of the biliary tract include malignant tumors that arise from the gallbladder, extrahepatic bile ducts, and ampulla of Vater (Fraumeni et al. 1996). Smoking-related excess risk for these tumors has been observed in a few case-control studies of women and men combined (Ghadirian et al. 1993; Chow et al. 1994; Moerman et al. 1994), but not in one other case-control study (Yen et al. 1987). Among women in CPS-II, risk for death from biliary tract cancers was lower among smokers than among women who had never smoked (Table 3.18). A nonsignificantly decreased risk for gallbladder cancer was observed in a Swedish follow-up study (Nordlund et al. 1997), but a Japanese cohort study reported a 30-percent excess mortality from this cancer among women who smoked (95 percent CI, 0 to 100 percent) (Akiba and Hirayama 1990). In a study of cancers of the extrahepatic bile duct and ampulla of Vater, the risk was three times higher among women who had smoked more than 50 pack-years than among women

who had never smoked, but women who smoked less than 50 pack-years had no excess risk (Chow et al. 1994). Estimates from both the Swedish and Japanese studies were based on a few cases and were imprecise.

Pancreatic Cancer

Studies have consistently demonstrated that smoking increases the risk for pancreatic cancer. Among women in CPS-II, the risk for death from pancreatic cancer was about twice as high among current smokers as among women who had never smoked (Table 3.18). A doubling of risk among women who smoked was also reported in the U.S. Nurses' Health Study (Fuchs et al. 1996) and the Iowa Women's Health Study (Harnack et al. 1997). Cohort studies from Ireland (Tulinius et al. 1997), Japan (Akiba and Hirayama 1990), Norway (Engeland et al. 1996), and Sweden (Nordlund et al. 1997) also indicated elevated risks for pancreatic cancer incidence or mortality among women who smoked. In a large case-control study of pancreatic cancer in the United States, risk was twice as high among current smokers as among women and men who had never smoked. The RRs were similar among women and men and increased with both the number of cigarettes smoked and the duration of smoking (Silverman et al. 1994). The risk was elevated more than threefold among smokers who smoked 40 or more cigarettes per day for at least 40 years. Other investigators found similar elevations in RRs among women and men (MacMahon et al. 1981; Kinlen and McPherson 1984; Wynder et al. 1986; Cuzick and Babiker 1989; Muscat et al. 1997).

Studies that have included both women and men make clear that the excess risk for pancreatic cancer associated with smoking declines after smoking cessation, regardless of the number of cigarettes smoked or the duration of smoking (Mack et al. 1986; Howe et al. 1991; Silverman et al. 1994; Ji et al. 1995; Fuchs et al. 1996). Nonetheless, former smokers who stop smoking for more than 10 years may retain a 20- to 30-percent excess risk (Howe et al. 1991; Silverman et al. 1994). The risk associated with smoking is not explained by the confounding effects of alcohol consumption-another suspected risk factor (Velema et al. 1986). Up to one-third of pancreatic cancers among women may be attributable to smoking (USDHHS 1989b; Silverman et al. 1994).

Urinary Tract Cancers

Cancers of the urinary tract comprise only about 7 percent of all cancers, but their incidence is rising (Devesa et al. 1990, 1995). Bladder cancer accounts for about 67 percent of all urinary tract cancers, cancer of the renal parenchyma (renal cell cancer) 23 percent, cancer of the renal pelvis 5 percent, and ureteral and miscellaneous tumors 5 percent. For these cancers, male-to-female incidence ratios are 3.9 for bladder cancer, 2.3 for renal cell cancer, 2.3 for cancer of the renal pelvis, and 2.9 for cancer of the ureter.

Smoking is a significant risk factor for cancer of each part of the urinary tract (McLaughlin et al. 1996; Silverman et al. 1996). The transitional cell cancers of the lower urinary tract (renal pelvis, ureter, and bladder) are more strongly related to smoking than are the adenocarcinomas of the renal parenchyma (renal cell cancers). For cancers of the renal pelvis and ureter, risk increases markedly with the number of cigarettes smoked and the duration of smoking. Long-term smokers (>45 years) have up to a sevenfold excess risk (Ross et al. 1989; McLaughlin et al. 1992).

In CPS-II, mortality from bladder cancer among women was more than 100 percent higher among current smokers than among those who had never smoked (Table 3.18); mortality from kidney cancer was 30 percent higher. Similar excess risks from smoking were found for bladder cancer mortality or incidence among women in cohort studies from Japan (Akiba and Hirayama 1990), Norway (Engeland et al. 1996), and Sweden (Nordlund et al. 1997). In the largest studies of specific urinary tract cancers and smoking, the lowest RR among women was found for renal cell cancer (adenocarcinoma of the renal parenchyma) and the highest for cancer of the renal pelvis and ureter; the risk for bladder cancer was intermediate (McLaughlin et al. 1992, 1995b; Hartge et al. 1993) (Table 3.20). Dose-response patterns were found for each cancer site. For each of these cancers, the risk among former smokers was less than that among current smokers (Hartge et al. 1987, 1993; Ross et al. 1989; McLaughlin et al. 1992, 1995b; Silverman et al. 1996). Other studies confirmed these findings (McCredie et al. 1982; Morrison et al. 1984; Piper et al. 1986; Jensen et

al. 1988; Wynder et al. 1988; Burch et al. 1989; La Vecchia et al. 1990; Burns and Swanson 1991; McCredie and Stewart 1992; Nordlund et al. 1997; Yuan et al. 1998).

The large-scale studies described in Table 3.20 reported that, among women, the proportion of cancers due to smoking was 9 percent for renal cell cancer (McLaughlin et al. 1995b), 31 percent for cancer of the renal pelvis and 46 percent for cancer of the ureter (McLaughlin et al. 1992), and 32 percent for bladder cancer (Hartge et al. 1987, 1993). Other studies of renal cell cancer reported population attributable risks ranging from 14 to 24 percent among women (McLaughlin et al. 1984; McCredie and Stewart 1992).

Thyroid Cancer

Although thyroid cancer is often studied as a single entity, four principal histologic types are recognized: papillary, follicular (well differentiated), medullary, and anaplastic (poorly differentiated). Papillary thyroid cancer is the most common type (50 to 80 percent of thyroid cancers in a given series), and follicular thyroid cancer is the next most common type (10 to 40 percent). Mortality from anaplastic thyroid cancer is high, but the five-year survival rates among patients with the other histologic types approach 95 percent (Ron 1996). Because papillary and follicular thyroid carcinomas occur more frequently among women than among men, women have a higher overall risk for thyroid cancer than do men.

Exposure to ionizing radiation is a well-established risk factor for thyroid cancer. Thyroid diseases such as goiter, thyrotoxicosis, and benign nodules have also been associated with an increased risk (McTiernan et al. 1984b; Preston-Martin et al. 1987; Ron et al. 1987; D'Avanzo et al. 1995b; Galanti et al. 1995b). Ahigh body mass index (BMI) may also be a risk factor (Ron et al. 1987; Goodman et al. 1992; Preston-Martin et al. 1993).

The higher incidence of thyroid cancer among women than among men suggests a causative role for female sex hormones. In fact, evidence indicated that estrogens probably act as late promoters of thyroid tumor growth in rodents (Mori et al. 1990). In epidemiologic studies of women, use of exogenous steroid hormones (OCs and hormone replacement therapy [HRT]) has inconsistently been associated with an increased risk for thyroid cancer (Franceschi et al. 1993), and reproductive history may be associated with risk (Preston-Martin et al. 1987, 1993; Ron et al. 1987; Franceschi et al. 1990; Kolonel et al. 1990; La Vecchia et al. 1993b; Levi et al. 1993; Galanti et al. 1995a; Paoff et al. 1995).

Investigations of smoking and risk for thyroid cancer have reported conflicting results. Studies that did not separate findings among women and men have not presented a consistent pattern (Ron et al. 1987; Sokic et al. 1994). Apparently no association exists specifically among men, but the data are scanty (Williams and Horm 1977; Kolonel et al. 1990; Hallquist et al. 1994). Among women, however, the majority of studies have found an inverse association between smoking and risk for thyroid cancer (McTiernan et al. 1984a; Kolonel et al. 1990; Hallquist et al. 1994; Galanti et al. 1996).

A Scandinavian case-control study has presented the most detailed data on smoking and thyroid cancer among women (Galanti et al. 1996). Risk was lower among premenopausal women who had ever smoked than among those who had never smoked (RR, 0.6; 95 percent CI, 0.4 to 0.96), particularly among those who started smoking before the age of 15 years (RR, 0.4; 95 percent CI, 0.3 to 0.8). Findings in this study also suggested a dose-response effect related to the number of cigarettes smoked per day and the duration of smoking. The results persisted after careful control of covariates such as reproductive history, use of exogenous hormones, and socioeconomic indicators.

One case-control study explored the association between maternal cigarette smoking during pregnancy and risk for thyroid cancer among their offspring (Paoff et al. 1995). More control mothers than case mothers smoked during pregnancy, but the investigators found no evidence of a dose-response relationship.

It is not clear why cigarette smoking would be associated with a reduced risk for thyroid cancer. Smokers have lower levels of thyroid-stimulating hormone than do nonsmokers (Bertelsen and Hegedüs 1994), and they could have a

lower thyroid cancer risk because of reduced thyroid stimulation. However, this mechanism should lead to a reduced risk among both women and men. Another possible explanation for a reduced risk among women is the antiestrogenic effect of smoking (Baron et al. 1990), which could counteract the excess risk due to estrogen-related stimuli among women. Identification of thyroid cancer and particularly of papillary cancers among young women is, however, largely influenced by the intensity of medical surveillance (Ron 1996). Because nonsmoking women are more health conscious than are smokers, their excess risk for thyroid cancer may be partially explained by enhanced diagnosis of the disease. This possibility may also explain the inconsistent results among former smokers.

Lymphoproliferative and Hematologic Cancers

Of the various hematopoietic malignant diseases, only acute myeloid leukemia has been consistently associated with smoking. RRs among smokers have ranged from 1.3 to nearly 3.0, but typically have been about 1.5 (Siegel 1983; Brownson et al. 1993; Kabat et al. 1994a). In CPS-II, women current smokers had an increased risk for mortality from myeloid and lymphoid leukemias (Table 3.18). A limited number of other studies presented gender-specific results. The excess risk for leukemia associated with smoking was similar among women and men in some of these studies (Williams and Horm 1977; Brownson et al. 1991), but in other investigations, the association was stronger among men (Garfinkel and Boffetta 1990; Friedman 1993). An upward trend in the risk for leukemia with increasing cigarette consumption was suggested in several studies (Kabat et al. 1994a), including one that reported separate data for women (Williams and Horm 1977). Limited evidence suggests that RRs may be reduced with increasing years of smoking cessation (Severson et al. 1990).

In general, multiple myeloma has not been associated with tobacco use (Garfinkel 1980; Boffetta et al. 1989; Brownson 1991; Heineman et al. 1992; Linet et al. 1992; Friedman 1993; Adami et al. 1998), although a few studies-generally those based on few participants-reported an increase in risk (Williams and Horm 1977; Mills et al. 1990). Findings specific among women are scant, but in both CPS-I and CPS-II, mortality from multiple myeloma was similar among women who smoked and among those who had never smoked (Garfinkel 1980) (Table 3.18). Two other cohort studies also found no association between multiple myeloma and cigarette smoking among women (Friedman 1993; Nordlund et al. 1997).

In some studies, investigators reported a modest excess risk for non-Hodgkin's lymphomas among smokers (Williams and Horm 1977; Franceschi et al. 1989; Brown et al. 1992; Linet et al. 1992; Zahm et al. 1997; De Stefani et al. 1998). In CPS-II, mortality from non-Hodgkin's lymphoma was slightly higher among women who smoked than among those who had never smoked (Table 3.18). However, other studies reported no substantial association (Hoar et al. 1986; Doll et al. 1994; Tavani et al. 1994b; McLaughlin et al. 1995a; Siemiatycki et al. 1995; Nelson et al. 1997; Herrinton and Friedman 1998). Some investigators proposed that smoking may confer higher risks among younger persons (Freedman et al. 1998) or among women (Zahm et al. 1997).

The association between Hodgkin's lymphoma and smoking has not been adequately examined. Some studies (Williams and Horm 1977; McLaughlin et al. 1995a; Siemiatycki et al. 1995; Mueller 1996; Nordlund et al. 1997; Pasqualetti et al. 1997) presented data regarding the relationship between smoking and the risk for Hodgkin's lymphoma, but the small number of cases prevents any conclusions. The risk for mortality from Hodgkin's disease was five times higher among women current smokers in CPS-II (Table 3.18) than among women who had never smoked, but this observation, based on only 10 deaths, lacks precision.

Conclusions

1. Smoking is a major cause of cancers of the oropharynx and bladder among women. Evidence is also strong that women who smoke have increased risks for cancers of the pancreas and kidney. For cancers of the larynx and esophagus, evidence among women is more limited but consistent with large increases in risk.

2. Women who smoke may have increased risks for liver cancer and colorectal cancer.

3. Data on smoking and cancer of the stomach among women are inconsistent.
4. Smoking may be associated with an increased risk for acute myeloid leukemia among women but does not appear to be associated with other lymphoproliferative or hematologic cancers.
5. Women who smoke may have a decreased risk for thyroid cancer.
6. Women who use smokeless tobacco have an increased risk for oral cancer.

Cardiovascular Disease

Cardiovascular diseases (CVDs) are disorders of the circulatory system, including diseases of the heart, cerebrovascular diseases, atherosclerosis, and other diseases of blood vessels. This group of diseases accounts for a greater proportion of deaths among women (42.3 percent) than among men (38.1 percent) (Murphy 2000). These disease processes interfere with the blood supply to important organs and can lead to serious clinical events such as myocardial infarction (MI; heart attack) and stroke. Impairment of the blood supply to the limbs can lead to pain and even a need for amputation. In this section, evidence on the relationship between smoking and the following cardiovascular conditions among women is reviewed: coronary heart disease (CHD), cerebrovascular disease, carotid atherosclerosis, peripheral vascular disease, abdominal aortic aneurysm, and hypertension.

Coronary Heart Disease

Smoking-Associated Risks

Each year, more than 500,000 women in the United States have an MI, and about one-half of them die from the event (Rich-Edwards et al. 1995). Despite a continuing decline since the 1960s in mortality from CHD, this condition still ranks first among the causes of death for middle-aged and older women (Eaker et al. 1993).

Epidemiologic data gathered during the past 40 years clearly point to the causative role of smoking in CHD: more than a dozen prospective studies indicated that women who smoke are at increased risk (Table 3.21). Studies in addition to those listed in Table 3.21 include the Tecumseh (Michigan) Community Health Study (Higgins et al. 1987), the Walnut Creek (California) Study (Perlman et al. 1988), and the Lipid Research Clinics Follow-up Study (Bush et al. 1987).

More than 20 years ago, smoking was recognized as a major independent cause of CHD among women-increasing their risk for CHD by a factor of about 2 (USDHHS 1980, 1983). The risk for CHD rises with the number of cigarettes smoked daily, the total number of years of smoking, the degree of inhalation, and early age at initiation of smoking. In the U.S. Nurses' Health Study, even women who smoked as few as one to four cigarettes per day had twice the risk for CHD as women who had never smoked (Willett et al. 1987; Kawachi et al. 1994); an analysis of data from that large cohort study after 14 years of follow-up found that 41 percent of coronary events in the study population were attributable to current smoking (Stampfer et al. 2000). Cigarette smoking acts together with other risk factors, particularly elevated serum cholesterol and hypertension, to greatly increase the risk for CHD. When the amount smoked and the duration of smoking are taken into account, the relative increase in death rates from CHD among smokers is similar for women and men, but the absolute increase in risk is higher among men (USDHHS 1983).

The effect of smoking on CHD risk among women seems to be relatively similar regardless of racial or ethnic group. In one study (Friedman et al. 1997) that included a substantial number of minority women, the age-adjusted RR for CHD mortality among current smokers compared with those who had never smoked was 2.3 ($p < 0.05$) for black women, 2.2 ($p > 0.05$) for Asian women, and 1.6 ($p < 0.05$) for white women. These RRs do not take into account the numbers of cigarettes smoked daily, so some differences in RRs may be due to differences in smoking patterns.

About 41 percent of deaths from CHD among U.S. women younger than 65 years of age and 12 percent among women older than 65 years have been attributed to cigarette smoking (USDHHS 1989b). Smoking has been associated with particularly high RRs among younger women (<50 years old) (Slone et al. 1978; Rosenberg et al. 1980a, 1985); consequently, the proportion of CHD cases attributable to cigarette smoking is high in this age group. According to one estimate in 1985, cigarette smoking may account for as much as two-thirds of the incidence of CHD among women younger than 50 years of age (Rosenberg et al. 1985).

More recent epidemiologic investigations have tended to report higher RRs for CHD among women who smoke than did earlier studies. For example, the 1989 Surgeon General's report on reducing the health consequences of smoking compared findings from the two ACS cohort studies conducted about 20 years apart (USDHHS 1989b). Both studies used identical sampling schemes. In the six-year follow-up of CPS-I in 1959-1965, the age-adjusted RRs for CHD among current smokers compared with those who had never smoked were 1.8 (95 percent CI, 1.7 to 2.0) among women aged 35 through 64 years and 1.2 (95 percent CI, 1.1 to 1.4) among women aged 65 years or older. In CPS-II, with follow-up during 1982-1986, the age-adjusted RRs for CHD were 3.0 (95 percent CI, 2.5 to 3.6) among women aged 35 through 64 years and 1.6 (95 percent CI, 1.4 to 1.8) among women aged 65 years or older. The latter findings were replicated in a six-year follow-up of CPS-II (Thun et al. 1997a).

Several factors could explain the higher RRs found in more recent studies of the association between smoking and CHD among women. These factors include the declines in overall cardiovascular mortality, as well as the higher number of cigarettes smoked daily and the longer duration of smoking among women in more recent years (Thun et al. 1997a). Early age at initiation of smoking is also associated with a markedly elevated risk for CHD, presumably because it is related to longer duration of smoking. In the U.S. Nurses' Health Study, early age at initiation was one of the strongest risk factors for CHD (Kawachi et al. 1994). Compared with women who had never smoked, women current smokers who started smoking before age 15 years had a RR of 9.3 (95 percent CI, 5.3 to 16.2). Even among women former smokers, the RR was 7.6 (95 percent CI, 2.5 to 22.5) for those who started smoking before age 15 years compared with those who had never smoked. The age at smoking initiation steadily declined for successive birth cohorts of U.S. women up to the 1960 birth cohort (see "Smoking Initiation" in Chapter 2). Data from the National Health Interview Survey (NHIS) indicated that the proportion of women who started to smoke before age 16 years increased from 7.2 percent among those born in 1910-1914 to 20.2 percent among those born in 1950-1954 (USDHHS 1989b). Thus, in more recent birth cohorts, duration of exposure to smoking has been longer because of early age at initiation.

The data on smoking cessation and CHD risk indicated a rapid, partial decline in risk followed by a gradual decline that eventually reaches the level of risk among persons who had never smoked (USDHHS 1990). The excess risk for CHD associated with smoking is reduced by 25 to 50 percent after 1 year of smoking abstinence; after 10 to 15 years of abstinence, the risk for CHD is similar to that of persons who had never smoked. Although most of the data were derived from white men, sufficient information is available about women to indicate that similar conclusions can be drawn for both genders (USDHHS 1990).

Studies of the effects of smoking cessation on the risk for CHD among women are summarized in Tables 3.22 and 3.23. The findings indicated a rapid decline in risk for CHD soon after smoking cessation. The case-control studies indicated a reduction of 30 to 45 percent in excess CHD risk among former smokers within one year of smoking cessation (Table 3.22). This reduction represents 35 to 70 percent of the eventual benefit (reduction in CHD risk) from permanent cessation. Similarly, two cohort studies (Omenn et al. 1990; Kawachi et al. 1994) found a 25-percent reduction in risk for CHD among former smokers within two years of cessation. This reduction represents one- third to one-half of the full potential benefit of cessation (Table 3.23).

These studies (Tables 3.22 and 3.23) also suggested that 10 years or more of smoking cessation must elapse before the risk for CHD among former smokers approaches that among persons who had never smoked. The case-control study by Dobson and colleagues (1991a) showed almost a complete reversal in risk after 3 years of cessation (RR, 1.3)

among former smokers, but the other data summarized in Tables 3.22 and 3.23 indicated that virtually complete reversal of risk is achieved only after more prolonged cessation.

Data from two studies (LaCroix et al. 1991; Paganini-Hill and Hsu 1994) that included women older than 65 years of age demonstrated that the benefits of smoking cessation also apply to older women. Indeed, the Established Populations for Epidemiologic Studies of the Elderly found a complete reversal in risk for CHD within five years of cessation (RR, 1.0; 95 percent CI, 0.5 to 2.1) (LaCroix et al. 1991). Risk declined among women who had stopped smoking either before or after 65 years of age. In contrast, the Leisure World Cohort Study found a significant difference in RR by age at cessation (Paganini-Hill and Hsu 1994). The study indicated that women who had stopped smoking at ages younger than 65 years had a RR for CHD mortality of 1.2 (95 percent CI, 0.9 to 1.5) and that women who had stopped at age 65 years or older had a RR of 1.6 (95 percent CI, 1.2 to 2.0).

Although the RR for CHD among current smokers tends to be lower for older persons than for younger persons, smoking cessation among older persons has a greater absolute effect because the rate of CHD is much higher in this group (USDHHS 1990). For example, in CPS-II, the RR for CHD mortality was 7.2 among women current smokers aged 45 through 49 years compared with women in the same age group who had never smoked; the corresponding RR among women aged 75 through 79 years was 1.6 (Thun et al. 1997c). However, the absolute difference in CHD mortality among smokers and nonsmokers aged 45 through 49 years was 23.8 deaths per 100,000 woman-years; among women aged 70 through 79 years, the difference was 316.6 deaths per 100,000 woman-years.

Some investigations have reported that persons who stop smoking tend to have smoked fewer cigarettes per day and to have started at an older age than those who continue to smoke (USDHHS 1990). In most of the studies discussed in this chapter, risk estimates were not adjusted for the number of cigarettes smoked per day before cessation or for age at smoking initiation-omissions that could lead to overestimation of the benefits of cessation (Kawachi et al. 1993a). In practice, however, such a bias does not seem to occur. In the U.S. Nurses' Health Study, the temporal pattern in reduction of CHD risk after smoking cessation was similar among women regardless of the number of cigarettes smoked per day before cessation, the age at smoking initiation, and other risk factors for CVD (Kawachi et al. 1994) (Table 3.23). Similarly, in a case-control study from Italy, Negri and colleagues (1994) reported that the time course of reduction in risk for acute MI after smoking cessation was similar among women and men who had smoked less than 30 years and among those who had smoked longer.

The benefits of smoking cessation seem to apply even among women with established coronary atherosclerosis. The Coronary Artery Surgery Study, which included 5,386 women evaluated by angiography (Omenn et al. 1990), showed that the time course of reduction in risk for CHD mortality after smoking cessation was similar among women with or without coronary atherosclerosis.

Smoking and Use of Oral Contraceptives

Epidemiologic investigation of the effects of oral contraceptives (OC) use on health is complicated because of changes in prescribing practices that resulted from early studies suggesting an association between OC use and CHD. Physicians may avoid prescribing OCs for women considered at increased risk for CHD, and heightened suspicion of disease in those who use OCs may have led to intensive investigation of symptoms (Stolley et al. 1989). Moreover, the composition of OC pills has changed over time. When OCs were introduced 30 years ago, they contained 150 µg of ethinyl estradiol and 10 mg of progestin, 5 and 10 times the current doses, respectively. As early as 1974, the estrogen component was as low as 20 µg in some preparations, but even in 1983 about one-half of OC prescriptions were still for formulations containing 50 µg or more of ethinyl estradiol (Mishell 1991). OCs now in widespread use in the United States contain 30 or 35 µg of estrogen (Petitti et al. 1996).

Studies conducted before the 1983 Surgeon General's report on smoking and CVD (USDHHS 1983) indicated that OC users had an increased risk for CHD (Stadel 1981; Sartwell and Stolley 1982). Overall, women who used OCs were reported to have about 4 times the MI risk of nonusers, but smokers who used OCs had a risk for MI about 10

times that of women who neither used OCs nor smoked (USDHHS 1983). In some studies, women who used OCs and smoked heavily (> 25 cigarettes per day) had up to a 40-fold increase in risk than did those who did not smoke or use OCs (Shapiro et al. 1979). Thus the risk from combined tobacco and OC exposure was greater than expected from the magnitude of the risk from OCs or smoking alone (Croft and Hannaford 1989).

The more recently available lower dose OC pills may be associated with a lower risk for CHD than are the higher dose preparations (Mant et al. 1987; Porter et al. 1987; Thorogood et al. 1991; Palmer et al. 1992; Sidney et al. 1998; Dunn et al. 1999). Nevertheless, studies continued to report a substantial excess risk for CHD among heavy smokers who currently use OCs (Rosenberg et al. 1985; Stampfer et al. 1988b; D'Avanzo et al. 1994; WHO Collaborative Study 1997) and indicated that the risk for MI associated with OCs may be concentrated among women who smoke (Stampfer et al. 1988b). In a case-control study of acute MI among women (Rosenberg et al. 1985), the RR was 3.1 (95 percent CI, 0.4 to 22.0) for current OC users who smoked 1 to 24 cigarettes per day compared with nonsmokers who used OCs. Among OC users who smoked 25 or more cigarettes per day, the RR was 23.0 (95 percent CI, 6.6 to 82.0). In the WHO Collaborative Study (1997), women who smoked 10 or more cigarettes per day and used OCs had a multivariate RR of 87.0 (95 percent CI, 29.8 to 254.0) compared with nonsmokers who did not use OCs. This elevation in risk is considerably greater than that which would be expected from the individual effects of smoking and OCs. The RR for MI associated with OC use among nonsmokers was 4.0 (95 percent CI, 1.5 to 10.4), and the RR for smoking 10 or more cigarettes per day among women who did not use OCs was 11.1 (95 percent CI, 5.7 to 21.8). Only exceedingly sparse data are currently available on the risk for CHD among smokers who use "third-generation" OCs-preparations containing 30 μg or less of ethinyl estradiol and either gestodene or desogestrel (Lewis et al. 1996).

The clinical recommendation has been that women who smoke, especially older women (e.g., >40 years), should be counseled against using OCs. A consensus panel reviewed the evidence on the health effects of OC use and smoking and recommended that women older than 35 years of age who smoke more than 15 cigarettes per day should not take OCs (Schiff et al. 1999). However, because cigarette smoking confers a higher risk for MI than does OC use, it may be more appropriate to advise women who use OCs to stop smoking (Hennekens and Buring 1985).

Smoking and Hormone Replacement Therapy

A meta-analysis of 31 case-control and cohort studies published before 1991 found a highly significant reduction in CHD risk (RR, 0.6; 95 percent CI, 0.5 to 0.6) for women who were taking HRT (Stampfer and Colditz 1991). Because smoking accelerates catabolism of oral estrogens, serum estrogen levels are lower among postmenopausal smokers who receive oral HRT than among nonsmokers who receive HRT (Jensen et al. 1985; Cassidenti et al. 1990). Consequently, the potential beneficial effects of HRT on CHD risk may be attenuated among smokers. This was indeed the case in one prospective study (Henderson et al. 1988), although the statistical significance of the finding was not addressed. In a case-control study, the protective effect of estrogen replacement therapy on fatal ischemic heart disease was similarly more marked among nonsmokers (Ross et al. 1981). In a case-control study of women aged 45 through 64 years, the protective effect of HRT on MI risk was also confined to nonsmokers (Mann et al. 1994). The RR among HRT users was 0.7 (95 percent CI, 0.5 to 1.0) for nonsmokers and 1.1 (95 percent CI, 0.7 to 1.5) for current smokers. However, smoking status was unknown for about one-half of the participants, and the data were more complete among case subjects than among control subjects.

A different interaction between HRT use and smoking status was reported from a 12-year follow-up study of 1,868 women aged 50 through 79 years who resided in a planned community (Criqui et al. 1988). Among HRT users, current smokers had a RR for CHD mortality of 0.4 (95 percent CI, 0.1 to 1.3), but former smokers had a RR of 2.3 (95 percent CI, 0.8 to 6.6); for women who had never smoked, the RR was 0.95 (95 percent CI, 0.5 to 2.0). In other studies, no substantial difference was observed in the effect of HRT between women who smoked and those who did not (Rosenberg et al. 1980b, 93; Grodstein and Stampfer 1998; Hulley et al. 1998).

Thinking about the role of estrogens in heart disease is now tempered by the results of a randomized clinical trial of estrogen plus progestin for the secondary prevention of heart disease (Hulley et al. 1998) and by very preliminary results from the Women's Health Initiative, a large trial that is investigating whether HRT affects risk for CVD and other outcomes (Kolata 2000). Contrary to expectation, both studies suggested the possibility of adverse cardiovascular effects. Thus, more evidence, including effects by smoking status, is clearly warranted. Regardless of any interaction between HRT and smoking, every woman who receives HRT should be counseled to stop smoking because HRT cannot negate the excess risk for CHD associated with cigarette smoking.

Cerebrovascular Disease

Smoking-Associated Risks

Stroke, the major form of cerebrovascular disease, is the third-leading cause of death among middle-aged and older U.S. women; it accounts for 87,000 deaths each year. Stroke is also the leading cause of severe disability and costs about $15.3 billion annually in medical care, including rehabilitation (Eaker et al. 1993). Smoking has long been recognized as a major cause of stroke (USDHHS 1989b). In CPS-II, 55 percent (95 percent CI, 45 to 65 percent) of deaths from cerebrovascular disease among women younger than 65 years and 6 percent of deaths from cerebrovascular disease among women aged 65 years or older were attributable to smoking (USDHHS 1989b).

In a meta-analysis of 32 studies of smoking and stroke that were published before May 1988, the overall RR for stroke among women and men current smokers was 1.5 (95 percent CI, 1.5 to 1.6) (Shinton and Beevers 1989). A strong dose-response relationship was found between the risk for stroke and the number of cigarettes smoked per day. Increased risks were found for subarachnoid hemorrhage (RR, 2.9; 95 percent CI, 2.5 to 3.5) and cerebral infarction (RR, 1.9; 95 percent CI, 1.7 to 2.2), but no increase in risk was found for hemorrhagic stroke (mainly intracerebral hemorrhage) (RR, 1.01; 95 percent CI, 0.8 to 1.3) or for intracerebral hemorrhage alone (RR, 0.7; 95 percent CI, 0.6 to 0.98). The estimate for hemorrhagic stroke was based on pooled data from only four studies and was strongly influenced by a single study that showed a marked inverse association with smoking (RR, 0.2 among men) (Bell and Ambrose 1982). In 26 studies, the number of women was sufficient to allow stratification by gender. In these data, the pooled risk for any stroke was slightly higher among women smokers (RR, 1.7; 95 percent CI, 1.6 to 1.9) than among men smokers (RR, 1.4; 95 percent CI, 1.4 to 1.5) (Shinton and Beevers 1989).

Subsequent studies generally have found a twofold to threefold excess risk for ischemic stroke and subarachnoid hemorrhage among women who smoked compared with women who had never smoked; the risk has been generally higher among heavy smokers (Tables 3.24 and 3.25). Apossible explanation for the increase in RR over time is that control of hypertension has improved in the United States during the past two decades. Thus, smoking is a more prominent risk factor for stroke than it was in the past (USDHHS 1990). An alternative explanation is that women who have recently reached the peak ages of stroke incidence tend to be heavier smokers than smokers in previous decades.

Although smoking is a clearly established risk factor for ischemic stroke and subarachnoid hemorrhage among both women and men, the relationship with primary intracerebral hemorrhage is less certain (Tables 3.24 and 3.25). One small population-based study found smoking to be a significant risk factor (Jamrozik et al. 1994). In contrast, a hospital-based, case-control study from Finland found that smoking was not an independent risk factor for intracerebral hemorrhage among either women or men (Juvela et al. 1995). In the U.S. Nurses' Health Study (Kawachi et al. 1993b), current smoking was associated with a multivariate-adjusted RR for cerebral hemorrhage of 1.4 (95 percent CI, 0.8 to 2.8) (Table 3.25). In the case-control study by Gill and colleagues (1989), current smoking was associated with an adjusted RR for cerebral hemorrhage of 1.3 (95 percent CI, 0.5 to 3.4) among women (Table 3.24) and 1.8 (95 percent CI, 0.9 to 3.7) among men. These data were based on few cases, however, because primary intracerebral hemorrhage tends to be the least common subtype of stroke among white women.

Smoking cessation has been reported to reduce the risk for both ischemic stroke and subarachnoid hemorrhage. After smoking cessation, the risk for stroke seems to return to the level of risk among those who had never smoked (USDHHS 1990). In some studies, the risk for stroke among women former smokers approached that of nonsmokers within 5 years of cessation (Wolf et al. 1988; USDHHS 1990 [CPS-II data for women in 50 states]). In other studies, 10 to 15 years of abstinence from smoking have been required (Rogot and Murray 1980; Donnan et al. 1989; USDHHS 1990 [CPS-II data for men in 50 states]).

Additional investigations since the late 1980s (Table 3.26) considered the relationship between duration of abstinence from smoking and the risk for stroke among women (Thompson et al. 1989; Kawachi et al. 1993b; Burns et al. 1997b; Friedman et al. 1997). In the U.S. Nurses' Health Study (Kawachi et al. 1993b), the risk for stroke among women former smokers approached the level of risk among women who had never smoked after 2 to 4 years of abstinence. The reduction of risk persisted after control for the number of cigarettes previously smoked daily, age at smoking initiation, and other known risk factors for stroke (data not shown). However, in a case-control study in the United Kingdom, only after 11 to 15 years of smoking cessation did stroke risk among female former smokers approximate that among women who had never smoked (Thompson et al. 1989).

In CPS-I, the risk for death from stroke among women former smokers approached that among women who had never smoked, at 15 to 19 years after smoking cessation (Burns et al. 1997b) (Table 3.26). The time it took for risk to decline differed by the number of cigarettes smoked daily before cessation (data not shown). For example, among women former smokers who had smoked fewer than 20 cigarettes per day, the risk approached that among women who had never smoked 5 to 9 years after cessation. Among former smokers who had smoked 20 or more cigarettes per day, an excess risk for stroke mortality persisted even after 20 to 24 years of cessation. A similar pattern was reported from a small study of men in the United Kingdom (Wannamethee et al. 1995).

In summary, the findings in most studies with data on women indicated that the increased stroke risk associated with smoking is reversible after smoking cessation. However, the duration of abstinence required for the excess risk to dissipate varied from 5 to 15 years.

Smoking and Use of Oral Contraceptives

Smokers who use OCs are at a significantly increased risk for stroke, especially subarachnoid hemorrhage, and part of this risk may result from the combined effects of smoking and OC use (USDHHS 1983). Studies published in the 1970s (Collaborative Group for the Study of Stroke in Young Women 1975; Petitti and Wingerd 1978) reported a particularly high risk for stroke among women who were heavy smokers and who used OCs; RRs ranged from more than 4.0 to 22.0. The dose of estrogen in OC preparations has been substantially reduced since then, and the risk for CVD associated with OC use and smoking may have changed from that observed for the early higher dose preparations (USDHHS 1990).

Most studies published since 1990 found that currently prescribed lower dose OC preparations are not associated with a substantially increased risk for stroke (Hirvonen and Idänpään-Heikkilä 1990; Thorogood et al. 1992; Lidegaard 1993; Lindenstrøm et al. 1993; WHO Collaborative Study 1996a,b; Schwartz et al. 1998). However, some studies reported that smoking increases the risk for stroke associated with OCs (Hannaford et al. 1994; Petitti et al. 1996; WHO Collaborative Study 1996a,b). For example, a multicenter, hospital-based, case-control study reported an adjusted RR for ischemic stroke of 7.2 (95 percent CI, 3.2 to 16.1) among current smokers who used OCs compared with nonsmokers who did not use OCs (WHO Collaborative Study 1996a). On the other hand, some data suggested no such interaction (Lidegaard 1993; Schwartz et al. 1998).

Smoking and Hormone Replacement Therapy

The data on the effects of HRT on the risk for stroke are sparse and inconsistent. Some investigators have observed a protective effect of HRT (Paganini-Hill et al. 1988; Finucane et al. 1993), others an increased risk (Wilson et al.

1985), and several no effect (Stampfer et al. 1991; Pedersen et al. 1997; Petitti et al. 1998).

A 12-year follow-up study of 7,060 women in the Copenhagen City Heart Study showed a statistically significant ($p < 0.04$) interaction between smoking status and HRT use (Lindenstrøm et al. 1993). HRT use appeared to be protective for stroke and transient ischemic attack (TIA) among current smokers but not among nonsmokers (both former smokers and women who had never smoked). Among current smokers who used HRT, the risk for stroke or TIA was about one-third the risk among women current smokers who did not use HRT. Among nonsmokers, however, HRT use was not associated with cerebrovascular events (RR, 1.0; 95 percent CI, 0.6 to 1.8). A similar pattern was observed in a population-based, case-control study of subarachnoid hemorrhage (Longstreth et al. 1994). In contrast, a more recent study found no interaction between HRT use and smoking in relation to stroke risk (Pedersen et al. 1997).

Carotid Atherosclerosis

Smoking is a major cause of carotid atherosclerosis, a marker of risk for TIA and stroke (USDHHS 1983). In several cross-sectional studies that included women, atherosclerotic lesions were more severe and diffuse among current smokers than among nonsmokers (Tell et al. 1989, 1994; Ingall et al. 1991). Ingall and colleagues (1991) reported results from a cross-sectional study of 1,004 patients (404 women) aged 40 through 69 years who had intracranial carotid artery arteriography. After adjustment for other cerebrovascular risk factors, duration of smoking was a strong predictor of the severity of atherosclerosis among both women and men. A similar finding was reported for severe atherosclerosis of the extracranial carotid arteries (Whisnant et al. 1990). In a study of 49 male and female pairs of identical twins discordant for smoking status, the total area of atherosclerotic carotid plaques was 3.2 times larger among smokers than among nonsmokers (Haapanen et al. 1989).

The association of smoking with carotid atherosclerosis persists with age. In a cross-sectional study of 5,116 participants (2,837 women) older than 64 years of age who were evaluated by ultrasonography, the prevalence of clinically significant (> 50 percent) stenosis of the internal carotid artery was 4.4 percent among persons who had never smoked, 7.3 percent among former smokers, and 9.5 percent among current smokers ($p < 0.0001$) (Tell et al. 1994). This study also showed a dose-response relationship between pack-years of smoking and mean thickness of the carotid artery wall ($p < 0.0001$). The difference in wall thickening among current smokers and persons who had never smoked was greater than the difference associated with 10 years of aging. In the Framingham study, an association was observed between time-integrated measures of smoking and carotid artery stenosis greater than 25 percent on ultrasound among both women and men. Smoking at the time of the examination was associated with stenosis only among women (RR, 2.6; 95 percent CI, 1.6 to 4.3) (Wilson et al. 1997).

A few prospective studies have evaluated the relationship between smoking and progression of carotid atherosclerosis. In a two-year follow-up of 308 apparently healthy women in France aged 45 through 55 years (Bonithon-Kopp et al. 1993), current smoking was a strong predictor of the development of new carotid atheromatous plaques, as assessed by B-mode ultrasound (multivariate-adjusted RR, 3.6; 95 percent CI, 1.5 to 8.7). A two-year follow-up of Finnish men similarly showed that pack-years of smoking was one of the strongest predictors of progression of carotid atherosclerosis (Salonen and Salonen 1990). More than 10,000 women and men were followed for three years in the Atherosclerosis Risk in Communities Study (Howard et al. 1998). Current smoking was associated with a 50-percent increase in the progression of carotid atherosclerosis.

Cessation of smoking appears to slow the progression of carotid atherosclerosis. In a cross-sectional study of 1,692 patients (829 women) admitted for diagnostic evaluation of the carotid arteries, the plaque measured by B-mode ultrasonography was 0.35 mm thicker among former smokers than among persons who had never smoked (95 percent CI, 0.17 to 0.54 mm). The plaque thickness of current smokers was 0.63 mm greater than that of persons who had never smoked (95 percent CI, 0.45 to 0.81 mm; $p < 0.001$ by multivariate analysis of variance). This finding suggested that the rate of progression of carotid atherosclerosis may be slower among persons who stop smoking than among continuing smokers (Tell et al. 1989).

Rogers and colleagues (1983) found significantly lower cerebral perfusion among long-term smokers than among nonsmokers; the reduction in cerebral blood flow was directly related to the number of cigarettes smoked daily. In a cross-sectional study, these investigators showed that smoking cessation was associated with a substantial improvement in cerebral perfusion within one year of cessation (Rogers et al. 1985).

Peripheral Vascular Disease

Peripheral vascular disease is associated with both functional limitations and increased risk for mortality. For example, in a 10-year follow-up study of 309 women and 256 men (average age, 66 years) with large-vessel peripheral arterial disease, the total mortality rate was 2.7 times higher (95 percent CI, 1.2 to 6.0) among women with large-vessel disease than among women free of disease. The corresponding RR for death from CVD was 5.7 (95 percent CI, 1.4 to 23.2) (Criqui et al. 1992).

Smoking is a strong, independent risk factor for arteriosclerotic peripheral vascular disease among women, and smoking cessation improves the prognosis of the disorder and has a favorable effect on vascular potency after reconstructive surgery (USDHHS 1980; Fowkes 1989). In general, the risk for intermittent claudication, a major clinical manifestation of peripheral vascular disease, has been reported to be lower among former smokers than among current smokers (USDHHS 1990). Among patients with established peripheral artery disease, smoking cessation has also been associated with improved performance (greater maximum treadmill walking distance and reduction of pain at rest), better prognosis (longer duration between initial and subsequent operations, lower amputation rate, and greater potency of vascular grafts), and longer overall survival (USDHHS 1990).

Studies published since 1990 continued to confirm a higher risk for peripheral vascular disease among smokers than among nonsmokers. Most studies were cross-sectional rather than prospective. However, in the 34-year follow-up of participants in the Framingham study (Freund et al. 1993), current smoking was a powerful predictor of intermittent claudication; RR was 2.3 (95 percent CI, 1.4 to 3.5) for current smokers compared with nonsmokers among women 45 through 64 years old. Among women aged 65 through 84 years, the RR was 2.2 (95 percent CI, 1.3 to 3.7).

The Edinburgh Artery Study (Fowkes et al. 1994) examined the ankle brachial pressure index (ABPI) in a random population sample of 783 women and 809 men aged 55 through 74 years. (The ABPI is a validated index inversely related to the degree of peripheral atherosclerosis.) In that study, lifetime history of cigarette smoking was correlated with lower ABPI among both women and men ($r = -0.27$; $p < 0.001$). Smoking was a stronger predictor of the prevalence of peripheral vascular disease than of CHD (Fowkes et al. 1992).

Epidemiologic studies are generally concerned with establishing the association of risk factors with clinical events, such as MI, stroke, or symptomatic peripheral vascular disease. The development of clinical disease is, however, the end point of a progression of pathophysiologic changes (Kuller et al. 1994). In the past, evaluation of the extent of atherosclerosis was limited to postmortem studies or to studies that used invasive techniques such as angiography. The advent of noninvasive diagnostic methods has made it feasible to study the extent of subclinical atherosclerosis in asymptomatic persons. Kuller and colleagues (1994) examined the relationship of smoking with subclinical atherosclerosis among 5,201 Medicare enrollees (2,955 women and 2,246 men) aged 65 years or older. Subclinical disease was defined as major electrocardiographic abnormalities, low ejection fraction or ventricular wall motion abnormality on echocardiogram, more than 25 percent stenosis or more than a 25-percent increase in wall thickness of the carotid artery or the internal carotid artery, decreased ABPI (< 0.9 mm Hg), and angina or intermittent claudication, as determined by a research questionnaire. In this cross-sectional study, current smoking was associated with increased risk for subclinical disease among women (RR for current smokers compared with nonsmokers, 2.0; 95 percent CI, 1.5 to 2.7) and among men (RR, 2.4; 95 percent CI, 1.6 to 3.6). In summary, current smoking among women is associated with increased risk for both clinical and subclinical peripheral vascular atherosclerosis. Smoking cessation is associated with improvement in symptoms, prognosis, and survival.

Abdominal Aortic Aneurysm

Smoking aggravates or accelerates aortic atheros clerosis, and the death rate for ruptured aortic aneurysm is higher among smokers than among nonsmokers (USDHHS 1983; Blanchard 1999). Excess risk for aortic aneurysm remains substantial even after 20 years' cessation of cigarette smoking (USDHHS 1983). Data for women are sparse; a previous Surgeon General's report summarized data from five prospective studies that examined the risk for death from aortic aneurysm; only two of these studies included data for women (Doll et al. 1980; USDHHS 1990, p. 242 [CPS-I tabulations]). Both studies found a higher risk for mortality from aortic aneurysm among women who smoked than among women who did not smoke.

In CPS-I (Burns et al. 1997b), the RR for death from abdominal aortic aneurysm was 3.9 among women current smokers compared with women who had never smoked. Risk increased with the number of cigarettes smoked; RRs were 3.5, 4.6, or 4.8 among women who smoked 1 to 19, 20, or 21 or more cigarettes per day, respectively. In a census-based cohort study in Japan that included 142,857 women aged 40 years or older, the RR for death from aortic aneurysm was 4.4 (90 percent CI, 2.7 to 7.3) among women current smokers compared with women who had never smoked (Hirayama 1990).

In a prospective study of 43 patients (10 women) who had small abdominal aortic aneurysms (diameter <5 cm), a median growth rate of 0.13 cm/year was recorded by serial ultrasound during follow-up (mean, three years) (MacSweeney et al. 1994). The growth rate was not associated with the initial diameter of the aneurysm, systolic or diastolic blood pressure, or serum cholesterol level. However, 30 of the 43 patients were current smokers, and smoking was associated with growth of the aneurysm. The median annual growth rate of aneurysms was 0.16 cm among smokers and 0.09 cm among nonsmokers ($p = 0.03$).

In a population-based cohort study, 758 women aged 45 through 64 years were examined by radiography for the development or progression of atherosclerotic plaques in the abdominal aorta, as indicated by calcified deposits (Witteman et al. 1993). After 9 years of follow-up, the investigators reported a dose-response association between atherosclerotic change and the number of cigarettes smoked per day. In a comparison with women who had never smoked, the multivariate-adjusted RR for development or progression of aortic atherosclerosis was 1.4 (95 percent CI, 1.0 to 2.0) among women who smoked 1 to 9 cigarettes per day, 2.0 (95 percent CI, 1.6 to 2.5) among women who smoked 10 to 19 cigarettes per day, and 2.3 (95 percent CI, 1.8 to 3.0) among women who smoked 20 or more cigarettes per day. Inhaling (compared with not inhaling) and duration of smoking were also statistically significant predictors of risk, after adjustment for intensity of smoking. The RR for aortic atherosclerosis declined after smoking cessation, but a residual excess risk among women former smokers compared with women who had never smoked was still apparent 5 to 10 years after smoking cessation (RR, 1.6; 95 percent CI, 1.1 to 2.2). These data are compatible with the reported slow reversibility of smoking-induced atherosclerotic damage in the abdominal aorta (USDHHS 1983).

Hypertension

Severe or malignant hypertension has been reported to be more common among women who smoke than among those who do not smoke (USDHHS 1980), yet epidemiologic and laboratory studies have produced conflicting results on the association between smoking and blood pressure. Several epidemiologic studies have shown that when blood pressure is measured in a physician's office, the readings among smokers are similar to or lower than those among nonsmokers, even after the lower BMI of smokers is taken into account (Greene et al. 1977; Gofin et al. 1982; Green et al. 1986). In contrast, laboratory studies have shown that cigarette smoking acutely raises blood pressure even among long-term smokers; the peak rise in blood pressure ranges from 3 to 12 mm Hg systolic pressure and 5 to 10 mm Hg diastolic pressure for a 20- to 30-minute duration of effect (Freestone and Ramsay 1982; Mann et al. 1989; Berlin et al. 1990; Groppelli et al. 1992).

Ambulatory measurement of blood pressure may clarify these results. Mann and colleagues (1991) compared blood pressure measurements taken in a physician's office with the 24-hour ambulatory blood pressure measurements for 77 women and 100 men with hypertension (diastolic blood pressure > 90 mm Hg) who were not receiving medication. Participants in this study were 26 women and 33 men who currently smoked at least one pack of cigarettes per day and 51 women and 67 men nonsmokers. Blood pressure readings taken in a physician's office were similar among smokers and nonsmokers (means, 141/93 vs. 142/93 mm Hg). However, the mean ambulatory systolic blood pressure was much higher among smokers than among nonsmokers (145 vs. 140 mm Hg; $p < 0.05$). Findings were similar among women and men. The lack of difference in physician's office readings for smokers and nonsmokers was attributed to abstinence from smoking during the minutes or hours preceding the blood pressure measurement. This explanation may also account for the lack of association between smoking and blood pressure measurements in epidemiologic studies, in which blood pressure is often assessed without consideration of time since the last cigarette. Similar findings on ambulatory blood pressure emerged from later studies of women and men (De Cesaris et al. 1992; Narkiewicz et al. 1995; Poulsen et al. 1998), but contrary data have also been reported (Mikkelsen et al. 1997). A study of salivary cotinine levels reported data consistent with higher blood pressure among smokers: higher pressures among women and men with higher salivary cotinine levels (Istvan et al. 1999). These findings also suggested that the effects of smoking on blood pressure are transient.

Conclusions

1. Smoking is a major cause of coronary heart disease among women. For women younger than 50 years, the majority of coronary heart disease is attributable to smoking. Risk increases with the number of cigarettes smoked and the duration of smoking.
2. The risk for coronary heart disease among women is substantially reduced within 1 or 2 years of smoking cessation. This immediate benefit is followed by a continuing but more gradual reduction in risk to that among nonsmokers by 10 to 15 or more years after cessation.
3. Women who use oral contraceptives have a particularly elevated risk of coronary heart disease if they smoke. Currently evidence is conflicting as to whether the effect of hormone replacement therapy on coronary heart disease risk differs between smokers and nonsmokers.
4. Women who smoke have an increased risk for ischemic stroke and subarachnoid hemorrhage. Evidence is inconsistent concerning the association between smoking and primary intracerebral hemorrhage.
5. In most studies that include women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5 to 15 years of abstinence, the risk approaches that of women who have never smoked.
6. Conflicting evidence exists regarding the level of the risk for stroke among women who both smoke and use either the oral contraceptives commonly prescribed in the United States today or hormone replacement therapy.
7. Smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women. Smoking cessation appears to slow the rate of progression of carotid atherosclerosis.
8. Women who are current smokers have an increased risk for peripheral vascular atherosclerosis. Smoking cessation is associated with improvements in symptoms, prognosis, and survival.
9. Women who smoke have an increased risk for death from ruptured abdominal aortic aneurysm.

Chronic Obstructive Pulmonary Disease and Lung Function

Chronic obstructive pulmonary disease (COPD) is a term defined differently by clinicians, pathologists, and epidemiologists, and each discipline uses different criteria based on physiologic impairment, pathologic

abnormalities, and symptoms (Samet 1989a). The hallmark of COPD is airflow obstruction, as measured by spirometric testing, with persistently low forced expiratory volume in one second (FEV_1) and low ratio of FEV_1 to forced vital capacity (FVC) (FEV_1/ FVC), despite treatment.

COPD may include chronic bronchitis characterized by a chronic cough productive of sputum with airflow obstruction, and emphysema accompanied by airflow obstruction. Emphysema is defined as "a condition of the lung characterized by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis" (American Thoracic Society 1987, p. 225). However, like bronchitis, emphysema is not consistently associated with airflow obstruction. Chronic bronchitis and emphysema with airflow obstruction are both included in the clinical diagnosis of COPD, but other lung diseases associated with airflow obstruction are specifically excluded from the clinical definition of COPD; these include asthma, bronchiectasis, and cystic fibrosis.

In epidemiologic studies, the diagnosis of COPD may be derived from surveys or databases. Questionnaire responses that may be used to diagnose COPD include reports of symptoms (e.g., dyspnea, cough, and phlegm), reports of physician diagnoses (e.g., emphysema, chronic bronchitis, or COPD), or both. Spirometry is often performed in epidemiologic studies to provide objective evidence of airflow obstruction among subjects with or without symptoms. Sources of data for descriptive or analytic studies of COPD include databases containing hospital discharge information or vital statistics (e.g., from death certificates). The standard terms used for COPD in these databases include terms from the *International Classification of Diseases,* ninth revision (*ICD-9)* (USDHHS 1989a)-"chronic bronchitis" (*ICD-9,* item 491); "emphysema" (*ICD-9,* item 492); and "chronic airways disease not otherwise classified" (*ICD-9,* item 496). The quality of these data sources may vary greatly.

Gender-specific differences have been observed in the likelihood of having a diagnosis of COPD, and it is unclear whether these differences result from diagnostic bias or reflect true gender-related differences in susceptibility. For example, in the Tucson (Arizona) Epidemiologic Study of Obstructive Lung Diseases, Dodge and colleagues (1986) found that, among subjects aged 40 years or older with a new diagnosis of asthma, emphysema, or chronic bronchitis based on self-report, women were more likely than men to receive a physician diagnosis of asthma or chronic bronchitis, and men were more likely to receive a diagnosis of emphysema. In the same population, Camilli and colleagues (1991) reported that a diagnosis of obstructive airways disease was stated on the death certificates of only 37 percent of 157 patients who had this diagnosis before death and that the proportion was lower among women (28 percent) than among men (42 percent).

Spirometric testing provides the most objective basis for diagnosing COPD. Among persons with a diagnosis of mild disease based on spirometric testing, reporting of obstructive airways disease on the death certificates was slightly higher among women (45 percent) than among men (34 percent), whereas for those with moderate-to-severe disease, reporting was higher among men (81 percent) than among women (57 percent). (For mild disease, the criteria were $FEV_1/FVC < 65$ percent and predicted FEV_1 50 to 70 percent of that in the normal reference population. For moderate-to-severe disease, the criteria were $FEV_1/FVC < 65$ percent and predicted $FEV_1 < 50$ percent of that in the normal reference population.)

Evidence suggested that changes in the structure and function of small airways (bronchioles) are fundamental for the development of smoking-induced COPD (Wright 1992; Thurlbeck 1994). An inflammatory process of the small airways (respiratory bronchiolitis) develops in all cigarette smokers; but in susceptible smokers, this process progresses and causes narrowing of these airways (Bosken et al. 1990; USDHHS 1990; Aguayo 1994). The inflammatory process may extend into the peribronchiolar alveoli and destroy the alveolar walls, which is the hallmark of emphysema. The rate of expiratory airflow depends on elastic recoil forces from the alveoli and on the diameter of the small airways. Complex interactions between changes in the structure and function of small airways and lung parenchyma result in the physiologic finding of chronic airflow limitation.

Cigarette smoking as a cause of COPD was extensively reviewed in earlier reports of the Surgeon General (USDHHS 1980, 1984, 1989b, 1990). (In the 1980 and 1984 Surgeon General's reports, COPD was referred to as chronic obstructive lung disease [COLD'.) In the 1980 Surgeon General's report on the health consequences of smoking for women (USDHHS 1980), the major conclusions relevant to COPD were as follows: (1) The death rate for COPD among women was rising, and the data available demonstrated an excess risk for death among women who smoked compared with nonsmokers, with a much greater risk for heavy smokers than for light smokers. (2) Women's overall risk for COPD appeared to be somewhat lower than men's, a difference possibly due to differences in previous smoking habits. (3) The prevalence of chronic bronchitis increased with the number of cigarettes smoked per day. (4) Evidence on differences in the prevalence of chronic bronchitis among women and men who smoked was inconsistent. (5) The presence of emphysema at autopsy exhibited a dose-response relationship with cigarette smoking during life. (6) A close relationship existed between cigarette smoking and chronic cough or chronic sputum production among women, which increased with total pack-years of smoking. (7) Women current smokers had poorer pulmonary function, by spirometric testing, than did women former smokers or nonsmokers, and the relationship was related to the number of cigarettes smoked.

In the 1984 Surgeon General's report on smoking and COPD (USDHHS 1984), the major additional conclusions relevant to morbidity and mortality from COPD among women were as follows: (1) Cigarette smoking was the major cause of COPD mortality among both women and men in the United States. (2) Both male and female smokers were found to develop abnormalities